KARL-HENRIK GUSTAVSON

DOWN'S SYNDROME

A CLINICAL AND CYTOGENETICAL INVESTIGATION

UPPSALA 1964

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FROM THE INSTITUTE FOR MEDICAL GENETICS
OF THE UNIVERSITY OF UPPSALA, SWEDEN
Head: Professor J. A. Böök, M.D., Ph.D.

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BY

KARL-HENRIK GUSTAVSON

A PUBLICATION FROM
THE INSTITUTE FOR MEDICAL GENETICS
OF THE UNIVERSITY OF UPPSALA
SWEDEN

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PRINTED IN SWEDEN BY

Almqvist & Wiksells

BOKTRYCKERI AKTIEBOLAG

UPPSALA 1964

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PREFACE

The present study was carried out at the Institute for Medical Genetics, University of Uppsala. I wish to express my sincere thanks to Professor Jan Arvid Böök, M.D., Ph.D., who suggested this investigation on the basis of the data available at the institute in May 1960. His encouragement and generous support throughout the course of this investigation are gratefully acknowledged.

I am also greatly indebted to the members of the scientific as well as the technical staff of the Institute for Medical Genetics, Uppsala. In particular, I am much obliged to Mr. Elvir Lander, B.A., for statistical aid. Furthermore, I would like to thank Leonard Atkins, M.D., Department of Pathology, Massachusetts General Hospital, Boston, for the linguistic correction of the manuscript and for valuable criticism.

I am grateful to the following collegues who kindly referred patients reported in this study: Professors Anna-Lisa Anell, M.D., Hans Forssman, M.D. and Bo Vahlquist, M.D., Uppsala; Associate Professor Bengt Hagberg, M.D., Uppsala; and Professor John Lind, M.D., Associate Professor Ingvar Alm, M.D., and Gunnar Klackenberg, M.D., Stockholm. I am also indebted to many collegues from hospitals throughout Sweden who have referred patients to me.

I am grateful to Associate Professor Jan Lindsten, M.D., Stockholm, who generously put some chromosomally investigated patients at my disposal.

Furthermore, I would like to thank Professor L. S. Penrose, M.D., F.R.S., University College, London, for the analysis of the palm and foot prints of some of the patients.

This investigation is part of a research programme on clinical cytogenetics supported by grants to Professor Jan A. Böök from the Swedish Medical Research Council, the U.S. National Institutes of Health (Research Grant No. B-4320) and the Founda-

tions Fund for Research in Psychiatry, New Haven, Conn., U.S.A. Furthermore, this work has been supported by grants to the author from the Medical Faculty of the University of Uppsala, the Prenatal Research Fund of the Stockholm newspaper "Expressen" and Kristiane and O. F. Hedström's Memorial Fund, which are gratefully acknowledged.

INTRODUCTION

Historical Review

In his classical paper of 1866 "Observations on an ethnic classification of idiots", Langdon Down gave the first comprehensive description of mongolism. He observed that certain classes of the mentally deficient had similar peculiarities which seemed to place them within definite ethnological families. Thus he characterized the mongoloid as a representative of the mongolian race. Twenty years earlier Séguin had given a description of mongolism, which he considered a sub-group of cretinism.

In 1876 Mitchell presented a summary of notes on his 62 cases of mongolism. These notes were accompanied by a report by Fraser giving a perfect description of a woman with mongolism. Ireland in his book "Idiocy and Imbecility" (1877) recognized mongolism as a special type of mental deficiency. Shuttleworth (1886) regarded mongolism as a condition of arrested development and characterized the affected children as "unfinished". He also remarked that "in our experience, nearly half these children are the last born of a long family".

The knowledge regarding mongolism increased steadily through a number of publications which covered such characteristics as the mouth and jaws (Jones, 1890), the eye signs (Oliver, 1891), the special conditions of the hands (Smith, 1896) and the relationship between mongolism and congenital heart defect (Garrod, 1898).

Sutherland (1900) called attention to certain similarities between mongolism and cretinism in infancy. He discussed typical examples of each condition and listed the similarities and differences. A comparative study of myxedema, mongolism and micromelia was made by Kassowitz in 1902.

In the subsequent years mongolism became accepted as a clinical entity and a vast amount of literature has been published about

the disease. In 1909 Shuttleworth in England presented a general review on mongolism. Brousseau and Brainerd in their American monograph of 1928 gave a review of the previous literature and of their series of patients. Geyer from Germany published a treatise in 1939 on the etiology of mongolism. A Spanish monograph was published by Schachter in 1943 and an English one by Engler in 1949. Benda in the U.S.A. published a book in 1946 (second edition 1949) followed by "The Child with Mongolism (Congenital Acromicria)" in 1960. Øster's thesis entitled "Mongolism" (1953) was based on a large unselected series of patients from Denmark. He gave a thorough and detailed review of the previous literature on mongolism. Hanhart (1960*a*) published a monograph on mongolism in Switzerland.

Langdon Down regarded mongolism as a regression to the Mongolian race. The chief exponent of this theory was Crookshank (1924). Further studies did not support this theory as mongolism was found to occur in all races and the resemblance of the affected to normal oriental peoples is superficial.

Some workers believed that mainly exogenous factors were responsible while others regarded mongolism as probably genetically determined. (See review of literatur by Øster, 1953.)

It had long been suspected that Down's syndrome could be associated with a chromosomal aberration by analogy with plants and experimental animals (Waardenburg, 1932; Bleyer, 1934; Turpin *et al.*, 1937; Penrose, 1939). At that time the cytological techniques were inadequate for a detailed analysis of the human chromosomes. With the use of improved cytological techniques, Tjio and Levan in 1956 demonstrated that the normal human chromosome number was 46. In 1959 Lejeune, Gautier and Turpin reported that in mongolism the chromosome number was 47 with an extra small acrocentric chromosome. This was the first proven chromosomal abnormality in man and was soon after confirmed by Böök *et al.* (1959), Ford *et al.* (1959) and Jacobs *et al.* (1959).

Aim of the Present Investigation

The aim of the present investigation has been:

(1) to collect original data for an analysis of chromosomal aberrations in a Swedish sample of patients with mongolism,

(2) to examine the significance of karyotype analyses in diagnosis, particularly when an unequivocal diagnosis based on clinical examination could not be made,

(3) to analyse the association between clinical signs and the different types of aberrant karyotypes occurring in patients with mongolism,

(4) to examine other similar karyotype abnormalities in order to evaluate their significance in differential diagnosis.

Terminology

The disease under discussion was designated by Langdon Down, in 1866, as the "Mongolian type of idiocy". "Mongolism" unfortunately has since then been the most commonly used term for this disease and the patient is generally referred to as a "mongol" or a "mongoloid". Several alternative terms have been suggested.

Shuttleworth (1886) introduced the term "unfinished children". The term "mongoloid deformity" has been suggested (van der Scheer, 1927). The expression "acromicria" was first used by Schüller (1907) in order to emphasize the characteristic retardation in growth of the facial bones and the ends of the extremities as opposed to acromegaly. Penrose (1949 *a*) suggested "generalized foetal dysplasia" instead of mongolism.

The need for better expressions than the terms "mongolian idiocy", "mongolism", "mongoloid", etc. is urgent in view of the fact that these are misleading and imply a racial aspect of the condition. Because of this, a number of authorities suggested that designations such as Langdon-Down anomaly, Down's syndrome, congenital acromicria or trisomy 21 anomaly should be used to replace the term "mongolism" (Allen *et al.*, 1961).

In this work the disease under discussion will be referred to as "Down's syndrome".

SURVEY OF THE LITERATURE OF DOWN'S SYNDROM

Epidemiology

Most investigations concerning the incidence and prevalence of Down's syndrome have been undertaken in samples from the following types of populations: (1) newborns, (2) mentally defectives and (3) total population.

The incidence of Down's syndrome among newborns varies with different investigations between 0.45 and 3.4 per 1000 (Böök, 1953; cf. Böök and Fraccaro, 1956; Collman and Stoller, 1962).

This considerable variation is explained, at least in part, by variabilities in factors such as source of sample, the place and time covered by the survey, reliability of diagnosis, type of ascertainment, the age distribution of the child-bearing women in the population and whether the incidence is calculated on maternities, live births or total births.

In a review, Penrose (1954 *a*) quoted an incidence at birth of about 1.5 per 1000. Øster in 1956, suggested 1.7 per 1000 as the average incidence.

In an investigation of approximately 57,000 consecutive Birmingham births, including both live and stillbirths, McKeown and Record (1960) calculated the incidence of Down's syndrome identified within two weeks of delivery at 1.11 per 1000. Based on all data available 5 years after birth they estimated an incidence of 1.69 per 1000.

The prevalence of Down's syndrome in institutions for mental defectives has been calculated by several authors (cf. Øster, 1953). An extensive personal investigation of the inmates of all Swedish institutions for the mentally deficient by Forssman (1960) showed that 98 per 1000 had Down's syndrome. Allen and Kallman found

the same prevalence among all admissions to the New York State Schools for mental defectives (1957).

Forssman points out that for several decades Down's syndrome has been increasing in the institutions for mental defectives. He suggests that this increase is due to several factors such as the increased tendency to institutionalize more persons with Down's syndrome and increased life expectancy for individuals with Down's syndrome as compared to individuals with other forms of mental deficiency.

The prevalence of Down's syndrome in the general population has been calculated by several authors. Øster (1953) gives a figure of 0.25 per 1000 in Denmark. In an investigation of a relatively isolated North Swedish population Böök (1953) reported a prevalence of 1.1 per 1000.

Lewis (1929) found the prevalence of Down's syndrome among children aged 5–14 years in England to be about 0.25 per 1000. Twenty years later Penrose (1949 *b*) estimated the prevalence of the condition among children 10–14 years old in London to be about 0.5 per 1000.

In 1958 Carter, in an investigation in London and the Home Counties showed that the prevalence among ten-year-old children was 1 per 1000. This increasing prevalence of Down's syndrome in the population is likely to be due mainly to a decreasing mortality.

Twin Investigations

Several twin investigations have been reported (Øster, 1953; Allen and Kallmann, 1957; Collmann and Stoller, 1962). Monozygotic twins are usually concordant for Down's syndrome. However, a few examples of Down's syndrome occurring in only one of probable monozygotic twins have been reported (van Beukering and Vervoorn, 1956; Fanconi, 1962; de Wolff *et al.*, 1962). According to de Wolff *et al.* these cases could be explained by irregular division of the chromosomes after the fusion of the gametes in an early stage of blastogenesis. Dizygotic twins are almost always discordant (Smith, 1960). No twins concordant for

Down's syndrome have as yet been proven to be dizygotic by differences in sex or blood antigens. The literature contains data on four twin pairs concordant for Down's syndrome and usually referred to as dizygotic (Russel, 1933; MacKaye, 1936; Jervis, 1943; Nicholson and Keay, 1957) but only two (MacKaye, 1936; Nicholson and Keay, 1957) remain reasonably convincing after a critical evaluation of the reported data.

Maternal Factors

That children with Down's syndrome tend to be born at the end of sibships was observed as early as in 1876 (Mitchell, 1876). In 1909 Shuttleworth suggested that this could be either a maternal age effect or a parity effect. It was later shown that the increased frequency of births of children with Down's syndrome with increasing maternal age is independent of the fathers' age (Jenkins, 1933; Penrose, 1933) and order of birth (Penrose, 1934).

Øster (1953) found in his Danish survey that the mean age for the mothers at birth of the child with Down's syndrome was 35.1 years. In the Danish population the average age for parturient mothers was 28.7 years.

Collmann and Stoller (1962) found that the mean age of all parturient mothers in the state of Victoria, Australia, during the 1942 to 1957 period was 27.9 years, while that for mothers of children with Down's syndrome was 33.7 years. Table 1 shows the incidence of Down's syndrome in different age classes of the mothers. Böök *et al.* (1958) found in an investigation of congenital malformations in a Swedish sample of children, born to mothers aged 42 and over, a total incidence of 2.1 per cent. Although the incidence of Down's syndrome increases with maternal age, it is by no means uncommon for children with Down's syndrome to be born to young mothers (Øster, 1953; Collmann and Stoller, 1962). It has been suggested by Penrose (1951, 1961 *a*) that the incidence of birth of children with Down's

TABLE 1. *Birth incidence of Down's syndrome in a Danish series and an Australian series in different maternal age groups.*

Maternal age, years	Birth incidence of Down's syndrome (per cent)	
	Øster (1953)	Collmann and Stoller (1962)
10–14	—	0
15–19	0.061	0.043
20–24	0.069	0.062
25–29	0.070	0.083
30–34	0.114	0.115
35–39	0.358	0.350
40–44	1.030	0.993
45–49	1.780	2.200[a]
All ages	0.162	0.145

[a] Maternal age 45 years and over.

syndrome is bimodal with respect to maternal age. One peak is found at a maternal age of 27 and another occurs over the age of 40. Other investigators have also noted this bimodality (Collman and Stoller, 1962).

Øster (1953) showed that the pregnancy-free intervals preceding and following the birth of a child with Down's syndrome were longer than the interval between two normal pregnancies, which occurred either before or after the birth of the child with Down's syndrome. He also found that the interval between the time of marriage and the first pregnancy was longer when the first child was affected with Down's syndrome. After the birth of an affected child there was a significantly greater abortion rate (16.5 per cent) than before (9.7 per cent) (Øster, 1953). A high rate of abortions has been observed in other series of mothers of children with Down's syndrome (Ingalls *et al.*, 1957; Coppen and Cowie, 1960; Cowie and Slater, 1963).

Ek (1959) investigated mothers of children with Down's syndrome and found that their serum protein-bound iodine was significantly elevated in comparison to that of a control group.

Coppen and Cowie (1960) found, however, normal serum protein-bound iodine values in a group of mothers of children with Down's syndrome compaired with a control group.

Ek and Jensen (1959) studied the corticoid output in the urine of mothers of children with Down's syndrome. They found normal values for the 17-ketosteroids and the 17-ketosteroidogenic steroids. However, the values for fractions containing dehydroepiandrosterone and an ether-extractable tetrazolium-salt-reducing ketocorticoid were double the values found in a control group. Rundle *et al.* (1961) found that mothers who had borne children with Down's syndrome at 27 years of age and under had a significantly higher output of dehydroepiandrosterone than another group of mothers who had their affected child later in life. The authors connect these results with the previous findings of a raised androgyny score and biacromial diameter in younger mothers of children with Down's syndrome (Coppen and Cowie, 1960).

Clinical Data

Physical features

Down's syndrome is characterized by a combination of mental deficiency and several morphological characteristics. The clinical diagnosis of Down's syndrome is sometimes difficult because there is no one strictly pathognomonic feature characteristic of Down's syndrome. Penrose (1949 *a*) sets a minimum diagnostic standard of four characteristics from his priority list of seven. A more complete list of the cardinal signs is presented by Øster (1953).

The means for the birth weights and the weights during the first year of life of children with Down's syndrome are significantly lower than for normal children (Øster, 1953). In this connection it is worth mentioning that children with Down's syndrome often are born before term (Parker, 1950; Øster, 1953; Smith and McKeown, 1955). Individuals with Down's syndrome are usually shorter than normal, very few affected men and women becoming taller than 155 cm and 145 cm respectively (Øster, 1953).

The head

There is a marked deviation in the development of the skull. Individuals with Down's syndrome are usually brachycephalic with a higher cephalic index than normal people (Roche *et al.*, 1961). The fontanels are often large and the sutures broad in babies with Down's syndrome. The closure of the frontal suture is often delayed (Øster, 1953; Benda, 1960).

The typical face is flat and broad. Usually the bridge of the nose is flat. The mouth is often open and the tongue is frequently protruding. Spühler (1929), Filicori and Tomasini (1959) described macroglossia as a frequent phenomenon, whereas other investigators have found the tongue to be fairly normal in size (Benda, 1960). The mucous membranes of the tongue begin to be coarsely papillated from the third to ninth months and fissured during the third or fourth year (Thomson, 1907; Beidlemann, 1945).

The eruption of the teeth is often delayed, the teeth are often smaller than normal, abnormally shaped and show an irregular alignment (Øster, 1953; Benda, 1960; Spitzer *et al.*, 1961; Silimbani, 1962). The lips are frequently everted and furrowed, especially the lower lip. The palate is often high-arched and narrow (Jones, 1890; Øster, 1953; Levinson *et al.*, 1955). The maxilla is generally hypoplastic (Spitzer *et al.*, 1961).

The eye signs have always been a prominent feature of Down's syndrom. The flattened orbit is mentioned by Lowe in his survey of the eye signs in Down's syndrome (Lowe, 1949). The orbital ridges are often absent or only slightly developed (Øster, 1953). The palpebral fissures are somewhat narrow and often markedly oblique, slanting upward towards to lateral edge. In Europeans the palpebral fissures are usually horizontal or only slightly elevated laterally.

In children with Down's syndrome the medial corner of the eye is covered by a skin fold, known as "epicanthus" or plica marginalis fetalis. This form of epicanthus has no relationship to the eye fold (epicanthus tarsalis) seen in the Mongolian race. The plica marginalis in Down's syndrome is a fetal feature, still present at birth. It is not rare in normal newborns but usually

disappears during the first years of life. It also usually disappears in individuals with Down's syndrome but at a much slower rate (Eissler and Longenecker, 1962). The margins of the eyelids are often affected by blepharitis, which frequently develops into blepharoconjunctivitis (Øster, 1953; Levinson *et al.*, 1955). The iris in patients with Down's syndrome shows two main anomalies, namely peripheral speckling and decrease in stroma. These stigmata, which may also be seen in normals, are more pronounced and more frequent in individuals with Down's syndrome (Brushfield, 1924; Lowe, 1949; Donaldson, 1961). The speckling (Brushfield spots) is usually observed in blue irides only (Brushfield, 1924; Øster, 1953).

It is not uncommon to find lens opacities in individuals with Down's syndrome (Lowe, 1949; Øster, 1953; Spitzer *et al.*, 1961; Cullen and Butler, 1963).

Strabismus, usually convergent, and nystagmus are not uncommon in young children with Down's syndrome (Lowe, 1949; Øster, 1953; Benda, 1960). Refractive errors are common (Skeller and Øster, 1951).

Different ear anomalies are reported in individuals with Down's syndrome. A comparison of the distribution of free to attached ear lobes shows that the attached lobe is much more frequent in children with Down's syndrome compared to normal children (Beckman *et al.*, 1962 *a*). Prominent ears and folding of the upper part of the helix occur rather frequently in individuals with Down's syndrome (Beckman *et al.*, 1962 *a*).

The trunk

The neck is often short and broad (Øster, 1953; Levinson *et al.*, 1955) and many of the infants with Down's syndrome show laxity of the skin of the neck (Benda, 1960).

Thorax deformities, usually funnel breast or pigeon breast, are found in a minority of individuals with Down's syndrome (Kassowitz, 1902; Øster, 1953). There is increased susceptibility to infections.

The breasts are often small and infantile with a small nipple (Øster, 1953).

There is a high frequency of congenital heart defects in patients with Down's syndrome. The earliest publications concerning cardiac anomalies in individuals with Down's syndrome were primarily based on clinical observations, but the nature of the anomalies was seldom specified. Figures on the frequency with which congenital cardiac defects are found in Down's syndrome have been reported by many authors. These figures vary between 7 and 70 per cent of cases with Down's syndrome. Most reports, however, give figures between 12 and 44 per cent with an average of 19 per cent (Berg *et al.*, 1960).

Two factors which contribute to the percentage variations are the age distribution of the patients and the methods and criteria upon which the diagnosis of congenital cardiac anomalies are based. Of 141 children with Down's syndrome who were autopsied, 79 had a congenital heart lesion (Berg *et al.*, 1960). About 2/3 of all their cases of Down's syndrome dying in the first three years of life had congenital heart defects, compared to about 1/5 of the cases of Down's syndrome dying between the fourth to tenth years. In this series, the types of cardiac anomalies in the children with Down's syndrome were as varied as in the other children with congenital heart defects without Down's syndrome. Berg *et al.* found that persistent ostium primum, persistent ostium A–V commune, atrial septal defects of the ostium secundum type, and anomalies of the mitral and tricuspid valves were more frequent in the cases of Down's syndrome than in the children without Down's syndrome.

The abdomen is often distended and pendant. Umbilical hernia is a frequent finding according to Benda (1960). Levinson *et al.* (1955) found diastasis recti in 76 per cent of children with Down's syndrome. Øster (1953) states, however, that rectal diastasis and umbilical hernia do not seem to occur more frequently than in the normal population.

Genitalia

Nearly all males with Down's syndrome have a hypoplastic penis and often small testes. Undescended testes is a rather frequent finding and the scrotum is generally smaller than normal (Øster, 1953).

The labia majora in infants with Down's syndrome are frequently oversized and round, whereas the labia minora are underdeveloped or absent (Bleyer, 1937; Benda, 1960).

Extremities

Down jr. (1909) pointed out that short and broad hands, short metacarpals and phalanges, as well as a transverse crease in the palm are characteristic of individuals with Down's syndrome. This so-called four-finger line occurs rather frequently among individuals with Down's syndrome but is present in only a few per cent of normal individuals (Brander, 1940; Øster, 1953; Beckman *et al.*, 1962 *b*).

The hands of individuals with Down's syndrome are flat, pawlike and hypotonic. The thumb may be set at a lower position and the fingers are frequently shorter than normal. As early as 1896, Smith described the fifth finger as crooked and demonstrated by means of X-ray that the middle phalanx of that finger is shorter than normal. Penrose (1931) observed only one flexion furrow on the fifth finger in some individuals with Down's syndrome.

The feet of individuals with Down's syndrome are often short and clumsy. The most characteristic finding is, however, a well-marked gap between the first and second toes (Engler, 1949; Øster, 1953; Levinson *et al.*, 1955). There is sometimes a deep line originating from this gap on the plantar surface (Brushfield, 1925; Øster, 1953). Syndactylies of the toes are found in about 10 per cent of defectives with Down's syndrome (Øster, 1953; Beckman *et al.*, 1962 *a*). Retroposition of the 4th toe is relatively common (Beckman *et al.*, 1962 *a*).

Individuals with Down's syndrome show a marked variation from normal individuals in the frequencies of different palm,

finger and sole-print patterns (Cummins, 1939; Workman, 1939; Turpin and Lejeune, 1953; Ford Walker, 1957; Beckman *et al.*, 1962 *b*).

Hypotonia is a common finding in individuals with Down's syndrome. Øster found marked hypotonia in 21 per cent of his cases (1953). The hypotonia is more pronounced and more common in children than in adults with Down's syndrome. Levinson *et al.* (1955) found hypotonic muscles in 66 per cent of children with Down's syndrome below 17 years of age.

Hyperflexibility of the joints is also a frequent finding in persons with Down's syndrome. It decreases, however, with advancing age. Thus, Øster (1953) found hyperflexibility in 89 per cent of children with Down's syndrome between 0 and 4 years of age but only in 2.5 per cent of affected individuals over 40 years of age.

Skin

The distal parts of the extremities of especially adult individuals with Down's syndrome are very often mottled and sometimes cyanotic.

Red, rough and scaly cheeks are not uncommon in young children with Down's syndrome (Øster, 1953; Levinson *et al.*, 1955). Generalized rough and dry skin is found in increasing frequency with advancing age (Øster, 1953).

The hair of the head, which in the young individuals with Down's syndrome is smooth and soft, grows more sparse and rough with increasing age (Øster, 1953). The pubic and axillary hair, as well as the growth of beard in males, often seems sparse (Øster, 1953). Dutton (1962) states that the pubic hair of patients with Down's syndrome has a marked lack of curl.

X-ray observations

Most X-ray examinations of individuals with Down's syndrome have been done in order to study the development of the ossification centers. The development of the ossification centers is usually

normal and without any characteristic features (Øster, 1953). Spitzer *et al.* (1961) in X-ray examinations of the skulls of 29 patients with Down's syndrome, whose ages ranged from 8 to 49 years, found extreme thinness of the skull bones to be very common. A brachycephalic skull was seen in half of the patients. One-third of these cases had a persistent metopic suture, which is far in excess of its normal occurrence. The metopic suture is normally the first of the cranial sutures to close (Pendergrass *et al.*, 1956). Hypoplasia of the middle segment of the face involving the maxilla and nasal bones was a frequent finding. Another common finding was impaired development of the paranasal sinuses and mastoid air cells. Failure of the development of the frontal sinuses was noted in 24 of the 29 patients. 86 per cent of the patients showed dental developmental changes on X-ray with microdontia and shape anomalies being the most common.

Smith (1896) described the fifth finger as crooked in individuals with Down's syndrome and demonstrated by X-ray that the middle phalanx of the fifth finger often is hypoplastic. This was later confirmed by others (Stettner, 1921; Spühler, 1929; Hefke, 1940). The clinodactyly occurs most commonly at the distal interphalangeal joint (Thursfield, 1921; Roche, 1961).

Anomalies of the pelvic bones in infants with Down's syndrome were first described by Caffey and Ross (1956). The pelves in the infants with Down's syndrome, who were less than 3 months of age, were compared with the standard for normal pelves of the same age established in another investigation (Caffey *et al.*, 1956). There were two main diagnostic findings in the pelves of the infants with Down's syndrome. (1) Bilateral flattening of the lower edges of the ileums, which is measured quantitatively as the acetabular angles. (2) Bilateral widening and flaring of the iliac wings, which is measured quantitatively as the iliac angles. Both the acetabular and the iliac angles were reduced in the infants with Down's syndrome compared to the normal infants. An iliac index, which included both features, was defined as "the sum of both acetabular and both iliac angles divided by 2". This index, often called Caffey's index, was also significantly smaller in the infants with

Down's syndrome. Caffey and Ross reported in 1958 a more extensive investigation comprising 48 infants, age two days to 12 months, with Down's syndrome. In addition to reduced acetabular and iliac angles they found hypoplasia of the ischial rami and bilateral coxa valga to be characteristic of Down's syndrome. It is noted by the authors that the latter two features are not clearly recognized before 6 months of age. Caffey and Ross (1958) have concluded from their X-ray observations of the pelves of patients with Down's syndrome that the findings are diagnostic in about 80 per cent of the cases, suggestive in about 20 per cent and uncertain or normal in less than 5 per cent.

Kaufmann (1961) made X-ray examinations of the pelves in 62 patients with Down's syndrome and observed that the abnormal configuration of the pelvis persisted through life.

Motor development

The motor development is usually retarded. There is a great variability as to the age at which the child with Down's syndrome can hold up his head. Some of the children do so at 2 months of age, others not until the age of $2\,{}^{1}/_{2}$ years. (Levinson *et al.*, 1955). Levinson *et al.* (1955) found a great variability in the age at which the child with Down's syndrome could sit up. Some of the children sat up as early as the normal, 6 to 8 months; others did not sit up until they were 2 years old or even older. Most of the children, however, sat up by 12 months of age.

There is also a marked variation of the time when children with Down's syndrome begin to walk. A few can walk at 12 months of age, some not until 5 years of age or even later. Most of the children learn to walk between 2 and 3 years of age (Øster, 1953).

There is usually a delay in the acquisition of good motor control after children with Down's syndrome have started to walk, and great accuracy of motor control is rarely achieved (Benda, 1960).

Intellectual status

There is a great variation of the degree of mental retardation in individuals with Down's syndrome. In 880 registered cases of

Down's syndrome in New York, Malzberg (1950) found that 24.5 per cent were classified as idiots, 71.6 per cent were classified as imbeciles, and 3.8 per cent were classified as morons (0.1 per cent were unascertained).

Tredgold (1937) found that a majority of his patients with Down's syndrome were in the I.Q. range of 25 to 45, with a few merely feebleminded.

Opinions differ concerning the upper range of intelligence in Down's syndrome. I.Q. up to 74 has been measured (Lahdensuu, 1937) and M.A. up to 10.8 years (Potozky and Grigg, 1942). To estimate the upper limit of the intelligence range Dunsdon *et al.* (1960) selected 52 of 390 patients with Down's syndrome for intelligence testing as these appeared to have had a relatively higher mental level. Of those selected, 44 came for interview and testing. The highest I.Q. was 68. In the original sample of 390 the proportion of those with I.Q. scores of 45 and over was estimated to be 6–7 per cent and those with I.Q.s of 55 and over, 1–2 per cent.

A few patients with Down's syndrome have learned to read and write. Øster (1953) reported that about 4 per cent of the patients with Down's syndrome in his series could read with comprehension, and about 2 per cent of the patients in the same series could write.

Most individuals with Down's syndrome over 10 years of age understand when spoken to and most adults with Down's syndrome can speak (Øster, 1953). Speech development proceeds in the same manner as in normal children but begins later and progresses more slowly (Gesell and Amatruda, 1949; Øster, 1953). Articulation is generally poor, the voice being low and gutteral (Øster, 1953) and sometimes they speak so indistinctly that only their relatives are able to understand them.

Character and temperament

Mitchell (1876) in his description of 62 cases of Down's syndrome noted that "The mental state is as distinct, as peculiar, and as steady as the physical. If the patients were brought to-

gether, they would be found to resemble each other strikingly in personal appearance. But more than this, they would also be found to resemble each other in character, in capacity, in likings and dislikings, in habits, in defects, in aptitudes." As early as 1909, Shuttleworth observed faculty of mimicry, sense of rhythm and cheerfulness of individuals with Down's syndrome, but he emphasized at the same time that they may be stubborn. Øster (1953) stated that "The mongols are fond of playing, in which they display imagination. They have a well-developed faculty of observation and a pronounced gift of mimicry. They enjoy dancing, singing, and listening to music, are good-natured and sociable, but often stubborn."

Some biochemical data

Apart from a possible gene locus on the chromosome involved in Down's syndrome, concerned with alkaline phosphatase production in polymorphonuclear leucocytes (Alter *et al.,* 1962, 1963; Trubowitz *et al.,* 1962; O'Sullivan and Pryles, 1963) there is some evidence of a locus concerned with the production of the enzyme galactose-1-phosphate-uridyl-transferase on the same chromosome (Brandt, 1962; Brandt *et al.,* 1963).

There is some evidence that individuals with Down's syndrome have a defect in their tryptophane metabolism characterized primarely by a low urinary excretion of xanthurenic arid (Jérôme *et al.,* 1960; O'Brien and Groshek, 1962).

Fuller *et al.* (1962) found an increased serum uric acid in individuals with Down's syndrome and Lundin and Gustavson (1962) reported an increased urinary excretion of beta-aminoisobuturic acid in individuals with Down's syndrome. Individuals with Down's syndrome usually have an increased erythrocyte triiodothyronine uptake compared with control subjects (Kurland *et al.,* 1957; Jackim *et al.,* 1961).

The normal human chromosome complement

In May 1960 a conference was held in Denver, Colorado, to devise a system of nomenclature for human chromosomes. "It was agreed that the autosomes should be serially numbered, 1 to 22, as nearly as possible in descending order of length, consistent with operational conveniences of identification by other criteria. The sex chromosomes should continue to be referred to as X and Y, rather than by a number, which would be an additional and, ultimately, a superfluous appellation. It was generally agreed that the 22 autosomes can be classified into seven groups, distinction between which can readily be made.

"It is considered that no separate nomenclature for the groups is needed. It is considered that any group to which it may be necessary to refer will be a sequence of those designated by Arabic numerals. Hence, any chromosome group may be referred to by the Arabic numerals of the extreme chromosomes of the group, joined together by a hyphen, e.g., the group of the three longest chromosomes would be Group 1–3."

The two primary features for the identification of the individual chromosomes are relative length and centromere position, the latter usually being expressed as the arm ratio, that is the length of the longer arm relative to the shorter.

The "conspectus of human mitotic chromosomes" which was proposed at the conference, is known as the Denver system.[1]

The importance of the Denver Conference is that it established a common system of nomenclature of human mitotic chromosomes. The Denver system is on the whole still valid. Some details have, however, been discussed and some further morphological distinctions have been made. A meeting was held in London in August 1963 "to consider developments since the Denver Conference and to assess the degree to which these may have aided characterization of individual chromosomes or may have revealed inadequacies

[1] The Denver nomenclature of human mitotic chromosomes is used consistently in this work (*Lancet*, *1*: 1063, 1960; *Cerebr. Palsy Bull.*, *2*: 1, 1960).

in earlier identifications". For details on the identification of individual mitotic chromosomes the reader is referred to the proceedings of the London Conference on "The normal human karyotype", 1963.[2]

Chromosome studies in Down's syndrome

1. *Down's syndrome with 21-trisomy*

Lejeune, Gautier and Turpin reported in 1959 that children with Down's syndrome had 47 chromosomes instead of the normal number of 46.

The extra chromosome belonged to the group of small acrocentrics. These findings were shortly afterwards confirmed by Böök *et al.* (1959), Jacobs *et al.* (1959) and Ford *et al.* (1959).

Böök *et al.* (1959) observed that in the patients with Down's syndrome three of the chromosomes in group 21–22 were satellited and they concluded that Down's syndrome might be a result of trisomy involving autosome no. 21. They also concluded that "if the 47th chromosome found in patients with mongolism is the primary cause of the abnormal development it is more likely to be a third homologue than an accessory chromosome".

Certain preliminary observations of meiosis in a few male patients with Down's syndrome indicate the occurrence of trivalents suggestive of trisomy (Miller *et al.*, 1960).

The difficulty in distinguishing pair no. 21 from pair no. 22 is generally recognized (Penrose *et al.*, 1960; Ferguson-Smith and Handmaker, 1961; Källen and Levan, 1962). However, by common agreement the extra small acrocentric chromosome in Down's syndrome is generally referred to as no. 21. This agreement will be followed throughout this work. It is now well established that Down's syndrome is usually caused by trisomy 21 (Lejeune, 1960; Makino *et al.*, 1960; Böök, 1961; Lehmann *et al.*, 1962; Hyashi, 1963).

The trisomy in Down's syndrome can be caused by (1) primary

[2] *Cytogenetics*, 2: 264, 1963.

nondisjunction during meiosis; (2) mitotic nondisjunction (3) secondary nondisjunction.

Primary nondisjunction. Primary nondisjunction is strictly defined as the failure of the two members of a chromosome pair to separate from each other at one of the two meiotic divisions of gametogenesis. In 1913, Bridges observed the genetic results of nondisjunction in Drosophila and introduced the term. Today the use of the term nondisjunction is extended and applied as well to mitosis.

If nondisjunction of chromosome no. 21 occurs during spermatogenesis or oogenesis, gametes are produced which contain the haploid set of chromosomes plus or minus one chromosome no. 21.

The gametes containing two chromosomes no. 21 fertilized by normal gametes give rise to children with Down's syndrome. The fate of zygotes having 45 chromosomes and only one chromosome no. 21 is unknown. This type of monosomy could be lethal at an early fetal stage.

The well-known influence of maternal age on the incidence of Down's syndrome suggests that the error of meiosis occurs more often during oogenesis than during spermatogenesis. The mechanism of this influence is however unknown.

Mitotic nondisjunction of chromosome 21 at the first cleavage division of a normal zygote would give origin directly to two cells, one with 47 (trisomic 21) chromosomes and one with 45 (monosomic 21) chromosomes. No viable individuals monosomic for chromosomes 21 have as yet been reported. The cell monosomic for chromosome 21 would probably be inviable and the end result would then be an individual with 21-trisomy.

Mitotic nondisjunction of chromosome 21 after the first cleavage division of a normal zygote, or chromosome lagging at anaphase in a zygote originally trisomic for chromosome 21 would give as a final result a mosaic of the type normal/trisomy 21. Several individuals with normal/trisomy 21 mosaicism have now been reported (Aula *et al.,* 1961; Clarke *et al.,* 1961, 1963; Blank *et al.,* 1962; Hyashi *et al.,* 1962; Lindsten *et al.,* 1962; Nichols *et al.,* 1962; Richards and Stewart, 1962; Smith *et al.,* 1962; Edwards

et al., 1963; Hyashi, 1963; Zellweger and Abbo, 1963; Verresen *et al.,* 1963; Weinstein and Warkany, 1963). Although information is limited there seems to be a good deal of phenotypical variation in this type of chromosomal mosaic. Many of these patients seem to be less affected and have only a few of the symptoms found in Down's syndrome.

Nondisjunction at the first cleavage division of a trisomic 21 zygote would produce cells with 46 (normal) and 48 (tetrasomic 21) chromosomes while nondisjunction at a later cleavage division of a trisomic 21 zygote would give origin to a mosaic of the type 46 (normal), 47 (trisomic 21) and 48 (tetrasomic 21) chromosomes. The latter is the type of chromosomal mosaic reported by Fitzgerald and Lycette (1961).

Secondary nondisjunction. Individuals who are chromosomally unbalanced as a result of a previous nondisjunction may produce both normal and abnormal gametes. This event is called secondary nondisjunction. Theoretically, it would be expected that as a result of random disjunction 50 per cent of the gametes produced by an individual who is trisomic for chromosome 21 would have the normal haploid number 23 and 50 per cent of the gametes would have 24 chromosomes, including two no. 21 chromosomes.

Eleven confirmed cases of female patients with Down's syndrome have had children. Of these, five have given birth to five normal children and one has given birth to previable twins who did not have Down's syndrome (Sawyer, 1949; Sawyer and Shafter, 1957; Forssman and Thysell, 1957; Forssman *et al.,* 1961; Levan and Hsu, 1959; Mullins *et al.,* 1960; Thuline and Priest, 1961; Thompson, 1961; Priest *et al.,* 1963). On the other hand four other affected mothers have given birth to four children and one male fetus with Down's syndrome. (Lelong *et al.,* 1949; Rehn and Thomas, 1957; Stiles, 1958; Hanhart, 1960 *b*; Hanhart *et al.,* 1961; Thompson, 1961, 1962.) One child of a mother with Down's syndrome was an idiot, who could not be regarded as definitely having Down's syndrome (Schlaug, 1957).

Chromosomal investigations have been done on the case reported by Forssman *et al.,* one of Hanhart's two cases, the case of

Levan and Hsu, the case of Rehn and Thomas cited by Stiles and Goodman and by Johnston and Jaslov, and the previable twin pair reported by Thuline and Priest (Levan and Hsu, 1959, 1960; Forssman *et al.*, 1961; Stiles and Goodman, 1961; Thulin and Priest, 1961; Johnston and Jaslov, 1963). In all cases in which both mother and child are reported to have Down's syndrome and where chromosomes have been investigated the individuals involved have had 47 chromosomes with trisomy for chromosome 21. However, the normal children including the previable twins have had normal karyotypes. Trisomy 21 was found in the karyotype of the mother with Down's syndrome who gave birth to a male fetus with Down's syndrome (Thompson, 1962).

The total reported offspring of mothers with Down's syndrome is too small for a statistical analysis. However, the data are suggestive of a 50 per cent risk for Down's syndrome occurring in the child of an affected mother.

No males with Down's syndrome are known to have fathered children.

Individuals with normal/21-trisomy mosaicism could, through secondary nondisjunction, produce children with Down's syndrome if all or a part of a gonad contains germinal cells with an extra chromosome 21. The mosaic parent may, but need not, show signs or symptoms of Down's syndrome. Familial Down's syndrome and Down's syndrome which is probably independent of maternal age may then result from secondary nondisjunction in a mosaic parent. Such cases have been described (Blank *et al.*, 1962; Smith *et al.*, 1962; Edwards *et al.*, 1963; Weinstein and Warkany, 1963).

2. *Down's syndrome with translocation*

According to Penrose (1951, 1961 *a*) the distribution of maternal ages at the birth of children with Down's anomaly is bimodal with a minor peak at the average maternal age for normal controls and the major peak at a maternal age above 40 years.

Furthermore, when Down's syndrome is found in maternal (but not paternal) relatives, the mean maternal age at the birth of

affected children with Down's anomaly is significantly lowered (Penrose, 1951, 1961 *a*).

All these facts suggest that in a proportion of cases with Down's syndrome factors independent of maternal age are of importance.

Polani *et al.* (1960) karyotyped a girl with Down's syndrome who was selected because she was born to a young mother. There was no evidence of sibship concentration or familial inheritance. The girl had 46 chromosomes, but only four short acrocentric chromosomes were found instead of five as would have been expected in a female with Down's syndrome. There were only five chromosomes instead of six in the 13–15 group, but an additional submetacentric chromosome was found in the 6–12 group. This additional chromosome was thought to have originated through a reciprocal translocation between chromosomes 14 and 21. The authors considered that the child carried two visible normal chromosomes 21 and one additional chromosome 21 attached to chromosome 14 through a translocation. The parents of this patient had normal karyotypes (Carter *et al.*, 1960). Makino *et al.* (1960) found 46 chromosomes and a translocation of the same type in a girl with Down's syndrome born at a maternal age of 22 years.

Hamerton *et al.* (cited by Hamerton, 1962) investigated 14 children with Down's syndrome born to mothers 27 years old or under. One of the children had a translocation of the 13–15/21 type (Hamerton *et al.*, 1961 *a*). One had enlarged satellites on one of the small acrocentric chromosomes inherited from the mother. Twelve of the affected children were ordinary 21-trisomics. Breg *et al.* (1962 *a*) karyotyped 12 patients with Down's syndrome born to mothers less than 29 years old. Ten of them had 21-trisomy and two had 13–15/21 translocations.

Several other nonfamilial cases of Down's syndrome with presumptive 13–15/21 translocations have been published (Ellis, quoted by Penrose, 1962; Ellis and Penrose, quoted by Penrose, 1962; German *et al.*, 1962 *a*; Scherz, 1962; Sergowich *et al.*, 1962; Shaw, 1962; Dent *et al.*, 1963; Hyashi, 1963).

The presence of presumptive translocations also explains in some

instances the exceptional occurrence of several individuals with Down's syndrome in the same family. The first cytogenetical examination of such a family was made by Penrose *et al.* (1960). They reported a family with two affected offspring and one normal sib. The mother had had two miscarriages. Each child with Down's syndrome had a total of 46 chromosomes including a 13–15/21 translocation. The mother, maternal grandmother and sister, who were all phenotypically normal, each had 45 chromosomes with a translocation between a chromosome 21 and one of the chromosomes in group 13–15. Thus, in this family the translocation must have occurred at least as early as in the embryogenesis of the grandmother.

Shortly afterwards Carter *et al.* (1960) reported a similar family with familial Down's syndrome caused by a 13–15/21 translocation. Several other examples of familial Down's syndrome with 13–15/21 translocations inherited from the mother have now been reported (Buckton *et al.*, 1961; Ek *et al.*, 1961; Forssman and Lehmann, 1961, 1962; Atkins *et al.*, 1962; Biesele *et al.*, 1962 *a*; Lehmann and Forssman, 1962; MacIntyre *et al.*, 1962; Shaw, 1962).

The only known example of paternal transmission of a 13–15/21 translocation to a child with Down's syndrome is a nonfamilial case reported by Sergovich *et al.* (1962).

Analyses of parental age data on cases of Down's syndrome with a 13–15/21 translocation have shown that neither the father's nor the mother's age at the patient's birth differed significantly from parental ages at the time of birth in the general population (Penrose, 1962).

Another type of presumptive translocation in Down's syndrome involves chromosome 21 and one of the other small acrocentric chromosomes. The possibility of an isochromosome for the long arm of a chromosome 21 in some of these cases must also be considered. In the subsequent discussion whenever a 21/21 translocation is considered, it is understood that a presumptive isochromosome for the long arm of chromosome 21 is also a possibility. A number of nonfamilial cases of Down's syndrome with a probable 21/21–22 translocation have been reported (Fraccaro

et al., 1960; Penrose *et al.*, 1960; Benirschke *et al.*, 1962; Forteza Bover and Báguena Candela, 1962; Gustavson, 1962; Lehmann *et al.*, 1962; Migeon *et al.*, 1962; Penrose, 1962; Dent *et al.*, 1963; Edwards *et al.*, 1963; Pfeiffer, 1963).

Examples of familial Down's syndrome caused by a probable 21/21–22 translocation have been reported. Forssman and Lehmann (1962) reported a family with two affected children, where the father contributed a chromosome of this type on to his progeny. Hamerton *et al.* (1961 *b*) have reported two families with similar types of chromosomal abnormalities. In the first of these, neither of the two children with Down's syndrome were living. However, the mother had 45 chromosomes with a 21/21–22 translocation. In the second family there were two children with Down's syndrome. In this family the transmission appeared to be on the paternal side. A 21/22 translocation has been reported by Shaw (1962) to occur in at least three generations. Two first cousins with Down's syndrome, offspring of a brother and a sister carrying the 21/22 translocation, appeared in this family. Pfeiffer (1963) has reported a family where a translocation of the 21/22 type was transmitted from mother to son, from mother to daughter, from father to son and from father to daughter. The transmission of a 21/21–22 translocation is often through the father, and the mean age of fathers of newborns with the latter type of chromosomal anomaly is, according to Penrose (1962), higher than the mean age of parents of newborns with a 13–15/21 translocation or of parents in the general population.

An unusual translocation in a case of Down's syndrome where the translocation chromosome somewhat resembled a large acrocentric chromosome was reported by Zellweger *et al.* (1963). These authors considered the abnormal chromosome "to be the product of a 21/21–22 translocation with breakage of one arm and recombination of the fragment with the other arm or of the fusion of the long arm of a small acrocentric chromosome with the distal end of the long arm of another small acrocentric chromosome".

3. *Other chromosomal anomalies in individuals with Down's syndrome or in their families*

Down's syndrome and Klinefelter's syndrome have been seen both in the same individual and in different members of the same sibship. Eight patients with both conditions have been karyotyped. They all had 48 chromosomes with trisomy for chromosome 21 and an XXY sex chromosome constitution (Ford *et al.*, 1959; Lanman *et al.*, 1960; Lehman and Forssman, 1960*a*; van Gelderen and Hustinx, 1961; Hustinx *et al.*, 1961 (twins); Hamerton *et al.*, 1962; Milcou and Maicanesco, 1963).

Whether the association between Down's syndrome and Klinefelter's syndrome in the same individual is more than pure chance is not known. However, it is not too surprising as both conditions are correlated with increased maternal age, Down's syndrome more so than Klinefelter's syndrome (Lenz *et al.*, 1959; Penrose, 1961 *b*).

Two sibships in which Klinefelter's syndrome, Down's syndrome and twinning were present have been reported (Wright *et al.*, 1963). Benirschke *et al.* (1962) have described a family with the translocation type of Down's syndrome and Klinefelter's syndrome in the same sibship. One of two brothers reported by Breg *et al.* (1962 *a*) was sex chromatin positive with an XXY sex chromosome constitution. The other brother was sex chromatin negative with a probable XO/XY/XXY mosaicism. An aunt had Down's syndrome.

Miller *et al.* (1961) described the occurrence of leukemia, two individuals with trisomic 21 Down's syndrome and a sex chromosome abnormality (XXXXY) in separate members of different sibships of the same pedigree

Breg *et al.* (1962 *b*) have reported the association of the triple-X syndrome and Down's syndrome in two families. These patients were born to young mothers. A sibship with one girl with Down's syndrome (trisomy 21) and one girl with XXX/XXXX mosaicism was reported by Bergemann (1962). The mother and maternal grandmother also had an XXX/XXXX sex chromosome

constitution. A maternal aunt showed an XX/XXX/XXXX sex chromosome constitution. In the same paper another family is described where the mother had an XXXX sex chromosome constitution. She had given birth to one normal girl and one girl with Down's syndrome. The combination of 21-trisomy and an XXX sex chromosome constitution has been reported in a girl with retinoblastoma (Day *et al.*, 1963).

Sibships with a case of trisomic-21 Down's syndrome and a case of Turner's syndrome of the XO-type have been described (Zellweger and Mikamo, 1961; Johnston and Petrakis, 1963).

An XYY male with Down's syndrome and other anomalies among his progeny has been reported by Hauschka *et al.* (1962).

Gagnon *et al.* (1961) have reported a malformed newborn who had 48 chromosomes and was trisomic for chromosome 18 as well as for chromosome 21. A girl with both 13–15 trisomy as well as trisomy for chromosome 21 was found to have clinical features of both Down's syndrome and the 13–15 trisomy syndrome (Becker *et al.*, 1963).

4. *Down's syndrome and leukemia*

Several reports indicate that there is an increased frequency of leukemia in patients with Down's syndrome (Bernhard *et al.*, 1951; O'Connor *et al.*, 1954; Schunk and Lehmann, 1954; Bernhard *et al.*, 1955; Carter, 1956; Merrit and Harris, 1956; Krivit and Good, 1957).

Evidence for this association was given by Stewart *et al.* (1958), who showed that the incidence of Down's syndrome in a group of children developing leukemia is about 17 times as great as in a group of children selected at random from the general population. The increased incidence of leukemia in children with Down's syndrome has been confirmed by Holland *et al.* (1962).

Most cases of leukemia in patients with Down's syndrome are of the acute form. Children with Down's syndrome and acute leukemia who have been karyotyped usually show no chromo-

somal abnormalities apart from trisomy for chromosome 21 (Tough *et al.*, 1961; Wald *et al.*, 1961).

However, some patients with leukemia associated with Down's syndrome have shown other chromosomal abnormalities (Johnston, 1961; German *et al.*, 1962 *a*; Ross and Atkins, 1962; Lejeune *et al.*, 1963 *a*; Vincent *et al.*, 1963; Warkany *et al.*, 1963).

In a few families a tendency towards leukemia and to Down's syndrome or other conditions characterized by chromosomal anomalies has been reported (Baikie *et al.*, 1961; Buckton *et al.*, 1961; Johnston, 1961; Miller *et al.*, 1961; Miller, 1963; Thompson *et al.*, 1963).

In 1960 Nowell and Hungerford reported that an abnormal small acrocentric chromosome was present in cells from blood cultures of patients with chronic myeloid leukemia in place of one of the small acrocentrics. The term Philadelphia chromosome (Ph^1) was later introduced to designate the abnormal chromosome. It is thought that the Ph^1 chromosome originates in the hematopoietic system through loss of material from the long arm of chromosome 21 or 22. The association of the Ph^1 chromosome with chronic myeloid leukemia was later confirmed by others (Baikie *et al.*, 1960; Tough *et al.*, 1961, 1962).

There is a decreased lobulation of the polymorphonuclear neutrophil leucocytes in patients with Down's syndrome (Turpin and Bernyer, 1947). Mittwoch (1959) has shown that the incidence of drumsticks in the neutrophils is lower in females with Down's syndrome than in controls and that the low incidence can be regarded as the result of the lowered lobe count.

Baikie *et al.* (1960) believe that the same small acrocentric chromosome which becomes trisomic in Down's syndrome is also involved in cases of chronic myeloid leukemia because of the association of an increased frequency of leukemia and defective nuclear lobulation in Down's syndrome, indicating some disturbances in the hematopoietic mechanism.

Further evidence suggesting that the same chromosome is involved in Down's syndrome and chronic myeloid leukemia is the finding of an elevated leucocyte alkaline phosphatase activity in

Down's syndrome (Alter *et al.*, 1962, 1963; Trubowitz *et al.*, 1962; O'Sullivan and Pryles, 1963) where chromosome 21 is present in triplicate, and decreased leucocyte alkaline phosphatase activity in chronic myeloid leukemia (Valentine and Beck, 1951) which is associated with a loss of genetic material from a small acrocentric chromosome.

MATERIAL

Cytogenetical investigations of 109 individuals with Down's syndrome or suspected Down's syndrome have been made at the Institute for Medical Genetics in Uppsala since 1959. Another ten cases of Down's syndrome or suspected Down's syndrome were chromosomally analysed at the Department of Endocrinology and Metabolism, Karolinska sjukhuset, Stockholm by Associate Professor Jan Lindsten.

The material thus consists of a total of 119 individuals, who have been referred for chromosomal investigation from different clinics and institutions in Sweden (Table 2); 74 (62 per cent) of the cases came from pediatric clinics and 34 (28 per cent) came from institutions for mental defectives. Some of the patients had been diagnosed clinically as clearcut cases of Down's syndrome, and others were referred because there was a suspicion of Down's syndrome. In the patients of the latter group chromosomal investigation was made for diagnostic purposes.

The age of the patients at the time of chromosomal investigation varied from one day to 53 years (Appendix Tables I and II).

From Table 2, it is seen that the group of clearcut Down's syndrome consists of 62 individuals (T, Y and F in Appendix Table IV). Eighteen of the patients in this group have been studied because they were born to relatively young mothers (30 years of age or younger, Y in Appendix Table IV). Nine of the patients with clearcut Down's syndrome were investigated because they were examples of familial Down's syndrome (F in Appendix Table IV). One male with clearcut Down's syndrome was studied because of dwarfism (Case 41), another male because of the presence of radio-ulnar synostosis (Case 79), a third male because there were features of Klinefelter's syndrome present (Case 80) and a fourth case, a female, because of failure of development of

TABLE 2. *Survey of the cases investigated cytologically.*

The patient referred from	Clinical diagnosis				
	Suspected Down's syndrome	Typical clinical signs of Down's syndrome			Total
		Familial case	Young mother	Others	
Pediatric clinic	47	1	11	15	74
Home for mental defectives	4	4	7	19	34
Children's psychiatric clinic	6	—	—	—	6
Medical clinic	—	—	—	1	1
Private doctor	—	4	—	—	4
Total no.	57	9	18	35	119

the right breast (Case 47). Thirty-one patients with clearcut Down's syndrome were investigated in conjunction with other studies concerning Down's syndrome.

The group of patients with suspected Down's syndrome consists of 57 individuals (S in Appendix Tables IV and V). In this group 37 of the patients were 12 months old or younger when the chromosome investigation was made.

The familial cases of Down's syndrome were referred by physicians after a request was published in Svenska Läkartidningen (The Journal of the Swedish Medical Association) in 1960. Those patients, who were investigated because they were born to relatively young mothers or because Down's syndrome was suspected, were generally referred for chromosomal analyses from pediatric clinics.

In addition, four patients with multiple congenital malformations but not suspected to have Down's syndrome have been included since they were found to be of differential diagnostic interest to Down's syndrome, from a cytogenetical point of view.

Detailed information on the patients will be found in the case reports, figures and tables of the Appendix.

METHODS

Cytogenetical

Culture of skin cells

A skin biopsy obtained by surgical removal of a small piece of epidermis is collected in a test tube containing the culture medium. The culture medium for skin consists of 20 per cent pooled human serum, 35 per cent Parker's solution, and 45 per cent Hanks' balanced salt solution (containing phenol red as indicator) in a 100 ml mixture, to which 5 ml chicken embryo extract, buffered benzylpenicillin and dihydrostreptomycin are added.

The skin specimen is minced on coverslips in Petri dishes in a droplet of medium with a pair of sharp ophthalmological scissors. Fresh medium is then added. Three to five primary cultures are made from each biopsy. The Petri dish cultures are incubated at 37°C in plastic boxes which are continuously supplied with a humidified mixture of 5 per cent CO_2 in air. The cultures are routinely inspected by the use of a phase contrast inverted microscope. The time lag between the preparation of the culture and the first signs of growth is on the average 2 weeks for adult material and 1 week for biopsies from small children.

The morphology of the cells is of the fibroblast-like type, the cells being long and spindle-shaped.

When the cultures have started to grow the medium is replenished every third day, unless it is required more often as indicated by the change in color of the phenol red. Cells growing on the bottom of the Petri dish are trypsinized and subcultured in the following way:

A solution of trypsin (Difco 1 : 250) 0.05 per cent in Hanks' solution frees the cells from the glass in about 10 minutes at 37°C. The action of the trypsin is stopped by adding an equal amount

of medium. The resulting cell suspension is transferred to a siliconized centrifuge tube by a siliconized pipette and centrifuged at 400 r.p.m. for 10 minutes at 37°C. The supernatant is pipetted off and the cells are transferred to new Petri dishes by a siliconized pipette.

Culture of bone marrow cells

Bone marrow cells obtained by puncture are transferred directly into a silicone treated test-tube containing 3 ml medium and 3 drops of 1 per cent heparin (Vitrum). The medium consists of 40 per cent pooled human serum, 30 per cent Parker's solution and 30 per cent Hanks' balanced salt solution (containing phenol red as indicator) in 100 ml mixture, to which 5 ml chicken embryo extract, buffered benzylpenicillin and dihydrostreptomycin are added. One ml of the resulting cell suspension is plated into a Petri dish containing a glass coverslip and 2 ml of culture medium is added. The cultures are incubated at 37°C in a humidified mixture of 5 per cent CO_2 in air. The bone marrow cells attach themselves to the glass in about 24 hours and after 2 or 3 days many cells have a fibroblast-like appearance, but a wide variety of other cellular types are also present, mostly belonging to the hemic series. The cell population becomes more and more uniform and after about a week most of the cells are fibroblast-like.

After 3 days the coverslip with its attached cells is transferred to a Petri dish containing fresh medium for freeing the coverslip from debris and red cells which are abundant in the original suspension. The coverslip with its attached cells is processed for cytological examination, while the cells attached to the bottom of the Petri dish are trypsinized for subculture. Subculture is performed as described above for the skin cells. The medium is changed when required as indicated by change in color of the phenol red, usually every third day.

For culturing other tissues, except for blood, exactly the same method is used as described above for the culture of skin cells.

Chromosome preparations

To obtain a sufficient number of mitoses it is recommended to change the medium 18–24 hours before making the preparations. For hypotonic treatment the coverslip is transferred for 12–15 minutes to 0.7 per cent tri-sodium citrate solution, prewarmed to 37°C, and kept at room temperature. The cells are then fixed and stained simultaneously in a solution of 2 per cent natural orcein (Gurr) in 50 per cent acetic acid for 2 minutes. The coverslip is inverted on to a microscope slide and superfluous fluid removed with filter paper. The effect of the hypotonic treatment is checked in a microscope. Sometimes some manual squashing is necessary to spread the chromosomes fully. The preparation is then sealed with Krönig cement.

Culture of leucocytes

The method used in this investigation is a modification of that of Hungerford *et al.* (1959).

The technique is as follows.

About 15 ml of venous blood is withdrawn into a syringe containing a drop of heparin. The blood is transferred to a siliconized centrifuge tube containing three drops of heparin. To obtain rapid sedimentation of the red blood cells the centrifuge tube is allowed to stand in ice water about one hour. Thereafter the plasma containing leucocytes is transferred by means of a siliconized pipette to a 25 ml universal container. The tube containing the red cells is centrifuged at 4°C for 3–10 minutes at 500 r.p.m. to obtain additional leucocytes suspended in plasma. The plasma is divided into 2 ml aliquots which are transferred into culture bottles.

Four volumes of Parker's solution containing penicillin and dihydrostreptomycin are added to one volume of plasma. This will give a final nucleated cell count of 800–1500 cells per mm^3 in individuals with normal white-cell counts. Finally 0.2 ml Phytohemagglutinin is added to each culture bottle. The cultures are incubated at 37°C and shaken twice each day.

The maximum mitotic activity is generally found after 3 days of culture. Colchicine is added 2 hours before harvesting.

To harvest the culture the cell suspension is transferred to siliconized centrifuge tubes and centrifuged for 10 minutes at 700 r.p.m. The supernatant is pipetted off and the pellet of cells is resuspended in 6 ml of a hypotonic tri-sodium citrate solution (0.7 per cent) for 30 minutes at 37°C. The tubes are centrifuged for 5 minutes at 500 r.p.m., the supernatant is pipetted off, and the cells are fixed.

The fixative is a fresh mixture of 9 parts 60 per cent acetic acid and 1 part 1 *N* hydrochloric acid. Two to three drops of the fixative are added to the cell suspension without breaking up the button of cells for 6–10 minutes. The fixative is then pipetted off and the pellet of cells is resuspended in 2–4 drops of freshly filtered solution of 2 per cent natural orcein in 60 per cent acetic acid. Good staining is achieved after 15–20 minutes. A drop of the cell suspension is pipetted on to a microscopic slide. A coverslip is placed on the slide and superfluous fluid removed with filter paper. The effect of the hypotonic treatment is checked under the microscope. Sometimes light squashing is necessary to obtain a good spread of the chromosomes. The preparations are then sealed with Krönig cement.

In about 15 per cent of the blood cultures, slides were prepared by a modification of the technique described by Moorhead *et al.* (1960).

In this method the fixative is a 3 : 1 mixture of absolute methanol and glacial acetic acid. After addition of 1–2 ml of fixative for 15 minutes the button of cells is gently broken up and the cell suspension is allowed to remain 30 minutes to 24 hours. The tubes are then centrifuged for 10 minutes at 500 r.p.m. The fixative is then removed and the cells are resuspended in fresh fixative, the amount of fixative depending upon the quantity of cells present.

One drop of cell suspension is pipetted on to a clean slide that has been dipped in ice water. Excess of fluid is shaken off and the slide waved rapidly over a spirit-lamp to dry. The slides are

then stained with 2 per cent natural orcein (Gurr) in 50 per cent acetic acid for 20–30 minutes. After this the slides are mounted in Canada balsam or Euparal (Falters and Garnett) and examined under the microscope.

Sex chromatin staining

Buccal cells are obtained by scraping of the oral mucosa with a sharp aluminium spatula. The cells are immediately smeared on a glass slide, fixed in 95 per cent ethyl alcohol and stained with thionin according to the method of Klinger and Ludwig (1957).

Cells cultivated on coverslips are fixed in Kahle's fixative and Feulgen-stained.

Only heterochromatic bodies adjacent to the nuclear membrane are recorded as sex chromatin.

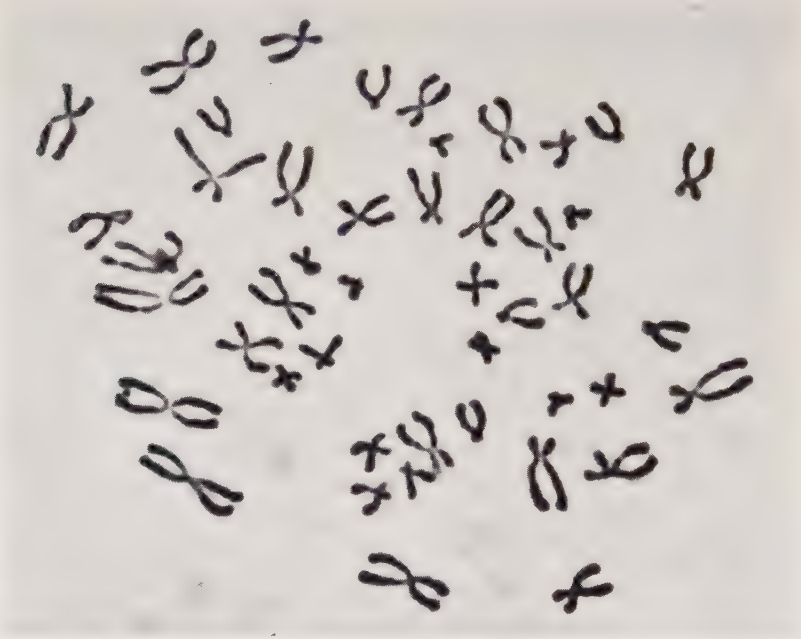


Fig. 1 *a*. Mitotic metaphase plate of a skin cell from a normal female. Acetic orcein stain. Phase contrast.

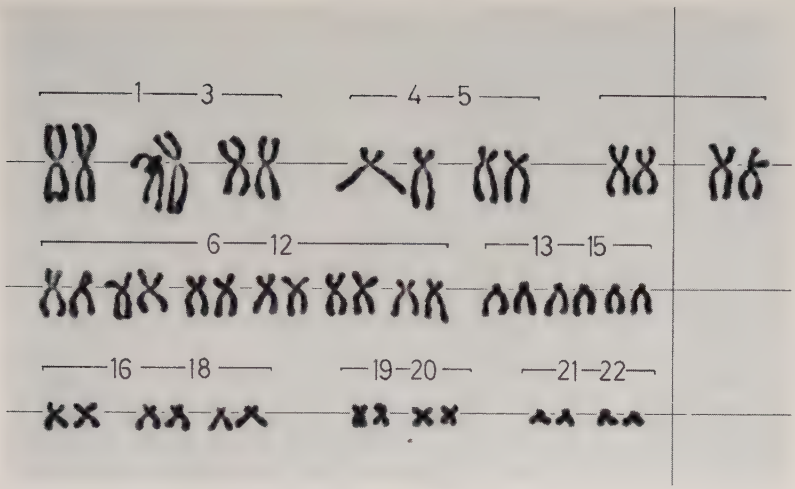


Fig. 1 *b*. Karyotype prepared from the metaphase plate shown in Fig. 1 *a*. The chromosomes are arranged in pairs and groups according to the Denver system. The sex chromosomes are to the right of the vertical line. Phase contrast, × 1400.

Procedure of analysis of chromosome preparations

The interpretation of the mitotic chromosomes as well as chromosome measurements were performed according to the Denver system.[1]

From each biopsy or blood sample, slides from at least two independent cultures are always analysed.

Certain criteria are used to select cells for chromosome analysis. Using a low-power magnification apparently undamaged cells in metaphase with good staining and fully spreading of the chromosomes are selected, care being taken that there are no other cells in metaphase in the vicinity. Once a cell has been selected for analysis it is not discarded. The cells are analysed with a high-power immersion lens. During the analysis a schematic drawing is usually made and the number of chromosomes is counted from

[1] The Denver nomenclature of human mitotic chromosomes is used consistently in this work (*Lancet 1:* 1063, 1960; *Cerebr. Palsy. Bull. 2:* 1, 1960).

Fig. 2 *a*. Mitotic metaphase plate of a skin cell from a normal male. Acetic orcein stain. Phase contrast.

the drawing. On each drawing the small acrocentric chromosomes and their satellites are noted.

When the chromosome number in a sufficient number of cells has been determined, the best quality metaphases are photographed (Figs. 1 *a* and 2 *a*). The chromosomes are cut out from enlarged photomicrographs and matched with the aid of simultaneous use of the microscope (Figs. 1 *b* and 2 *b*).

Distribution of chromosome counts

In analysing cells from individuals with only one modal number, a few cells with a chromosome number deviating from the

Fig. 2 *b*. Karyotype prepared from the metaphase plate shown in Fig. 2 *a*. The chromosomes are arranged in pairs and groups according to the Denver system. The sex chromosomes are to the right of the vertical line. Phase contrast, × 1600.

mode are sometimes recorded. The degree of variation depends largely on the quality of the preparation and on how rigid the selection of undamaged cells has been. All cells containing a deviating chromosome number are analysed in detail under the microscope and are also, as a rule, photographed and matched.

The distribution of chromosome counts was studied in cultured skin and bone marrow cells as well as in cells obtained from peripheral blood cultures of the ninety-four 21-trisomic individuals in this series. A total of 2648 cells, including 1050 skin cells, 290 bone marrow cells and 1308 peripheral blood cells, were used for this study (Table 3).

The proportion of cells with a chromosome count deviating from the modal number was small, 2.2 per cent, and is similar to the proportion of cells with a chromosome count deviating from the modal number found in blood cultures from normal females reported by de la Chapelle (1962).

In the material under discussion the hypomodal number of

TABLE 3. *Number of counted cells and the distribution of chromosome counts in cultured cells from blood, skin and bone marrow of 94 individuals with 21-trisomy.*

Type of tissue cultured	No. of biopsy specimens	No. of counted cells per individual			No. of cells with chromosome count				Total no. of counted cells
		Min.	Median	Max.	45	46	47	48	
Blood	46[a]	10	26	55	—	28	1280	—	1308
Skin	43	7	19	66	4	16	1027	3	1050
Bone marrow	16	4	14	40	2	4	282	2	290
Total	105	4	23	66	6	48	2589	5	2648
%	—	—	—	—	0.2	1.8	97.8	0.2	100.0

[a] In two individuals two biopsy specimens of the same tissue were taken and counted as one biopsy specimen.

counted cells was 54 (2.0 per cent) and the hypermodal number was 5 (0.2 per cent). The lower 99 per cent confidence limit of the hypomodal value of 2 per cent is 1.4 per cent and the upper 99 per cent confidence limit of the hypermodal value of 0.2 per cent is 0.5 per cent. The difference of 1.8 per cent between the hypomodal number and the hypermodal number is thus highly significant.

The nonmodal counts may represent either instances of somatic aneuploidy originally present or induced during cultivation, or artefacts resulting from technical errors during the preparation of the slides. The type of artefact which would give rise to hypomodal counts is breakage of the cell and loss of one or more chromosomes. If the lost chromosomes become included in neighboring cells a hypermodal count can be obtained.

Analysis of hypomodal cells usually cannot distinguish between those that result from artefacts and those that are produced by mitotic errors.

In the material under discussion the number of cells from peripheral blood with nonmodal counts is significantly lower than the number of cells with nonmodal counts derived from bone marrow ($P < 0.01$). Other comparisons in the distribution of chro-

mosome counts between cells from the three different tissues show no significant differences.

The distribution of chromosome counts in the cultured cells from the 16 cases of suspected Down's syndrome with an apparently normal karyotype was also studied (Appendix Table II). The percentage of aberrant cells was also found to be small in this group, only 1.8 per cent.

Case no. .... Surname .... Christian name .... Birth date .... Date of examination .... Birth dates of the parents ..... Data concerning pregnancy and delivery ..... Expected date of confinement .... Birth weight ..... height ..... head circumference ..... Order in sibship .... Abortions .....
Congenital malformations, mental retardation among close relatives .....
Consanguinity in parents or grandparents .....
Began to sit ..... stand ..... walk ..... speak single words ..... speak in sentences .....
be continent .....

Findings at present examination

Nutritional and developmental status ..... Height ..... Weight ..... Head circumference ..... length ..... width ..... Cephalic index ..... Sutures and fontanelles .....
Oblique palpebral fissures ..... Epicantic eye-folds ..... Blepharitis .... Brushfield spots ..... Flat nasal bridge .....
Mouth permanently open ..... Abnormal size, shape or alignment of teeth ..... Furrowed tongue ..... Protruding tongue ..... High-arched palate ..... Narrow palate ..... Folded ears ..... Short and broad hands ..... Short 5th fingers .... Type of four-finger line .... left/right ... Palm prints ..... Heart .....
Lungs ..... Abdomen ..... Hernia ..... Hyperflexibility of joints ..... Muscular hypotonia ..... Syndactyly ..... Gap between 1st and 2nd toes ..... Malformations ..... Motor development .....
Ability to understand when spoken to ..... speak in sentences .....
Ability without help to dress and undress ..... to eat without help .... continent? ..... Psyche .....
Photography .....
General impression regarding diagnosis of Down's syndrome .....

Fig. 3. Case Record Form.

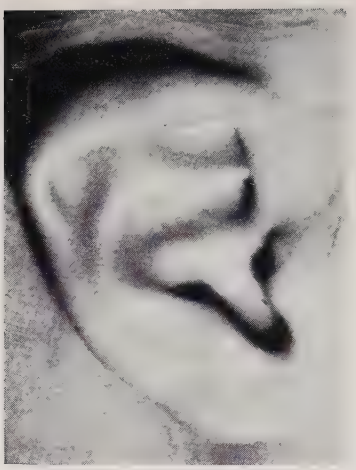


Fig. 4. Ear with angular folded upper helix from a patient with Down's syndrome.

Clinical

A standard case record form, which included data concerning family, birth, development and physical examination, was used (Fig. 3). Birth data and records from hospitals and institutions were examined. The data were later supplemented by interviews with close relatives, usually the parents. I have personally collected all the data and also done the physical examinations.

The normal range of body height for healthy Swedish females and males up to 2 years of age was obtained from the data of Karlberg and Perman (1959) and the range for the ages above 2 years was obtained from Broman *et al.* (1942).

The maximum head width, the maximum head length and the horizontal head circumference were measured according to the method of Martin and Saller (1957–1959). The cephalic index is defined as the ratio of the head width to length × 100. Penrose (1949*a*) classified individuals with Down's syndrome as brachycephalic if the cephalic index was 83 or more. The same criterion has been used in the present study.

"Folded ear" refers to an anomaly characterized by a folding

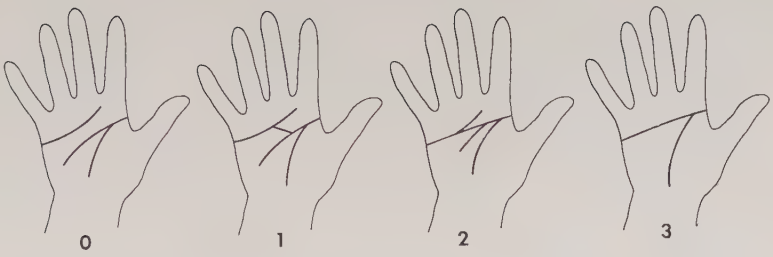


Fig. 5. Schematic drawing of palmar lines, 0, Normal; 1, Transitional type 1; 2, Transitional type 2; 3, Typical four-finger line.

outwards and downwards of the upper part of the helix of the ear (Fig. 4).

The fifth finger was classified as short if it did not reach the distal flexion furrow of the 4th finger.

The four-finger line has been recorded according to Brander (1940) as explained in Fig. 5.

Finger and palm dermal ridge patterns have been analysed according to the method used by Beckman *et al.* (1962 *b*).

X-ray films of the hands and pelvis were always evaluated by a radiologist. The methods described by Caffey and Ross (1956) were employed in the examination of the X-ray films of the pelvis.

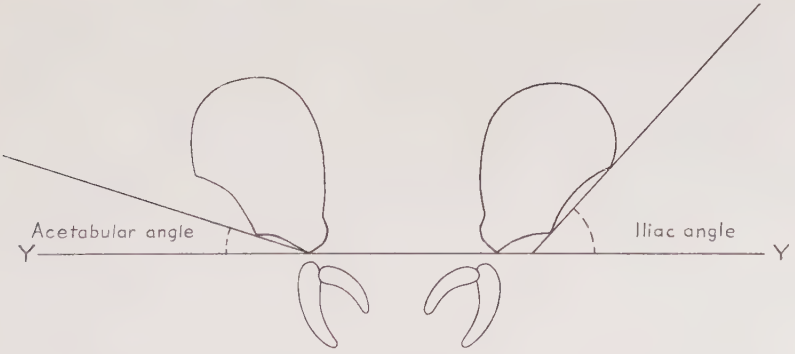


Fig. 6. Schematic drawing for measurement of the acetabular and iliac angles. Both angles are based on Hilgenreiner's line extending through both Y-cartilages.

The two characteristic findings in the pelvis of an infant with Down's syndrome are:

(1) Bilateral flattening of the lower edges of the ileums, which is measured quantitatively as the acetabular angle (Fig. 6).

(2) Bilateral widening and flaring of the iliac wings, measured quantitatively as the iliac angle (Fig. 6) (Caffey and Ross, 1958). An iliac index, often called Caffey's index, has been defined as the sum of the two acetabular and the two iliac angles divided by 2. Caffey's index in children with Down's syndrome or suspected Down's syndrome under the age of 12 months in the present material was compared with the standard for normal pelves of the same ages established in an investigation by Caffey *et al.* (1956) (Fig. 16).

RESULTS

Cytogenetical Findings

The cytogenetical data on the patients with chromosomal aberrations are summarized in Table I of the Appendix and the data on those with apparently normal karyotypes in Table II of the Appendix. For detailed analyses of the results, the patients have been divided into the following groups according to the chromosome constitutions: apparently normal karyotypes; the 21-trisomy group; mosaicism involving chromosome 21; the translocation group; other chromosome constitutions.

Apparently normal karyotypes

In the present series sixteen of the individuals with suspected Down's syndrome had apparently normal chromosome complements. Analyses of the cells with nonmodal counts showed no constant karyotypes.

The 21-trisomy group

Ninety-four of the patients were found to have 47 chromosomes with an extra small acrocentric chromosome. A representative karyotype is shown in Fig. 7. Analyses of the cells with chromosome counts deviating from the modal number of 47 showed no constant karyotypes. In 81 cases, cells derived from only one tissue were analysed: bone marrow cells from 10 patients, skin cells from 30 patients, and blood cells from 41 patients. In 12 cases cells derived from two different tissues were analysed, and in one case cells derived from three different tissues were analysed (see Table 4).

Mosaicism involving chromosome 21

Mosaicism was observed in two patients.

Case 45 was a chromosomal mosaic of the normal/trisomy 21

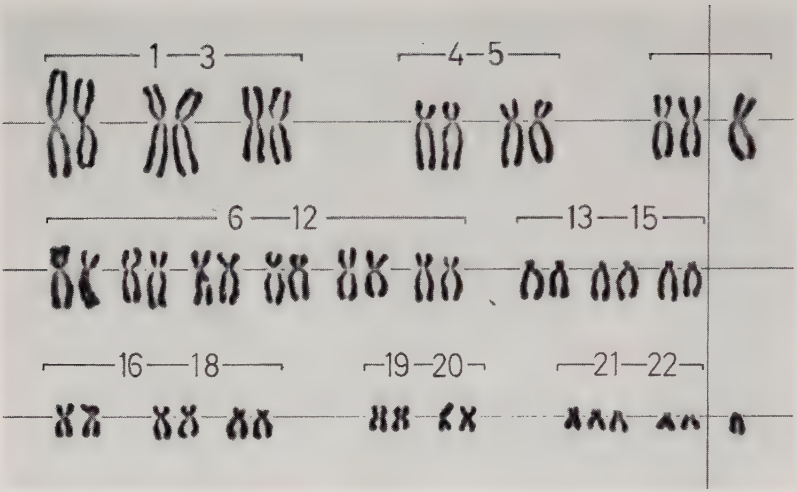


Fig. 7. Karyotype from a boy with Down's syndrome (Case 49). There are 47 chromosomes, including trisomy in the 21–22 group.

type. This patient has been described earlier (Lindsten *et al.*, 1962). The mosaic pattern was found consistently in two blood and three skin cultures. In all specimens examined there were two types of cells, one with 46 and the other with 47 chromosomes. The cells with 46 chromosomes had an apparently normal female karyotype and those with 47 chromosomes had an extra small

TABLE 4. *Number of different tissues karyotyped from 94 cases of Down's syndrome with 21-trisomy.*

Type of tissue cultured	No. of individuals	Total no. of counted cells
Blood only	41	1189
Skin only	30	712
Bone marrow only	10	188
Blood and skin	5	119+ 220
Skin and bone marrow	6	101+ 102
Skin and kidney	1	7+ 16
Skin, spleen and brain	1	10+ 14+ 20
Total no.	94	2698

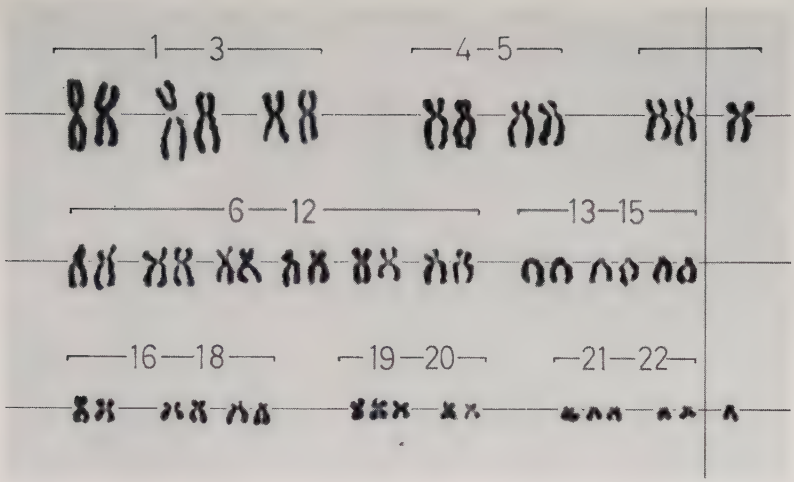


Fig. 8. Karyotype prepared from a mitotic skin cell of a boy with Down's syndrome (Case 29). There are 48 chromosomes, including an extra chromosome in each of groups 19–20 and 21–22.

acrocentric chromosome. A normal female sex chromatin pattern was consistently found in cells of the oral mucosa and in skin cells grown *in vitro*. The parents had normal sex chromatin patterns in buccal mucosa cells and apparently normal karyotypes in cells from peripheral blood cultures.

A chromosomal mosaic with three different cell types was found in Case 29. This case has previously been reported in a preliminary communication (Gustavson and Ek, 1961). The mosaic pattern was found consistently in cultures from two skin biopsies. Twenty-two per cent of the cultured skin cells contained 46 chromosomes and had a normal male complement; 38 per cent had 47 chromosomes with 21-trisomy; 40 per cent of the cells had 48 chromosomes and were trisomic for chromosome 21, and, in addition, had an extra chromosome similar to those of group 19–20 (Fig. 8). All cells from peripheral blood cultures were found to have 47 chromosomes with a 21-trisomy.

No sex chromatin was found in cultured skin cells from the patient. The parents had apparently normal karyotypes.

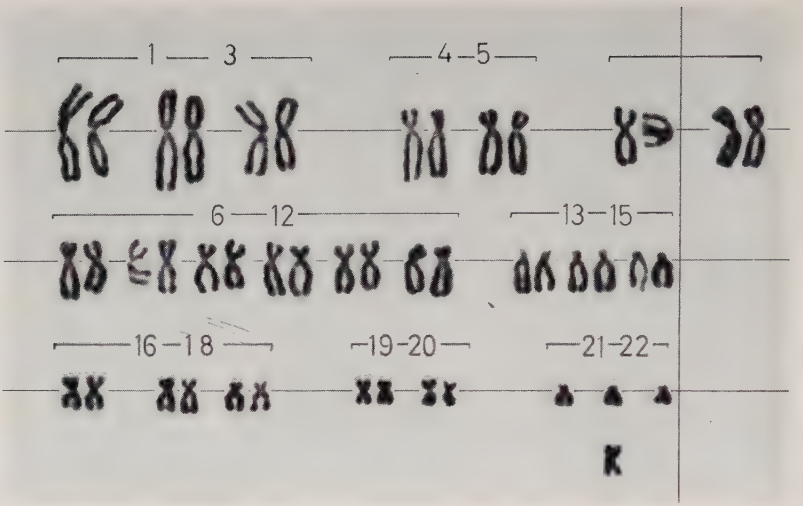


Fig. 9. Karyotype from a girl with Down's syndrome (Case 34). There are 46 chromosomes, including an odd chromosome placed below group 21–22. This chromosome is interpreted as the result of a 21/21–22 translocation or as an isochromosome for the long arm of chromosome 21.

The translocation group

Cases 34, 42, 88 and 102 showed a presumptive 21/21–22 translocation or isochromosome for the long arm of chromosome 21, and Case 62 had a presumptive 13–15/21 translocation.

Analysis of the chromosomes of Case 34 (previously reported by Gustavson, 1962), a girl, was based on the study of cell cultures derived from one skin and one bone marrow biopsy. The chromosome number was 46. There were, however, only three short acrocentric chromosomes instead of the normal four. Five chromosomes were found in group 19–20 instead of the four normally present (Fig. 9). The extra chromosome in group 19–20 could not be directly identified. It was however classified as the longest chromosome in this group. The relative lengths[1] of these five chromosomes were calculated from measurements of enlarged mic-

[1] The relative length is the length of the chromosome relative to the total length of a haploid set containing the X chromosome, times 1000.

rophotographs. Ten cells were analysed in this way. The relative length of the extra chromosome was 27 as compared with 24 for no. 19. A normal female sex chromatin pattern was found in the interphase nuclei of oral mucosa and cultured skin cells, respectively. Analyses of cultured blood cells from the parents showed apparently normal karyotypes. Analyses of cultured skin cells from the patient's only sib, a boy, showed a normal male karyotype.

Case 42, a girl, showed 46 chromosomes and a similar karyotype. Analysis of the chromosomes was based on the study of cells derived from skin and blood cultures. There were only three chromosomes in the 21–22 group but five chromosomes in the 19–20 group. The relative lengths[1] of the chromosomes were calculated from measurements of enlarged microphotographs of 10 cells. The relative length of the extra chromosome, which was classified as the longest chromosome in group 19–20, was 24 as compared with 23 for no. 19. A normal female sex chromatin pattern was found in cultured skin cells. Analyses of cultured blood cells from the mother showed a normal female karyotype. The father was unknown.

Case 88, a girl, showed also a presumptive 21/21–22 translocation or isochromosome for the long arm of chromosome 21. Analyses of the chromosomes were based on cultured blood cells. There were only three chromosomes in the 21–22 group. An extra metacentric chromosome was found in the (19–20) group. The relative lengths[1] of the chromosomes were calculated from measurements of enlarged microphotographs of 10 cells. The relative length of this extra chromosome, which was classified as the longest chromosome in group 19–20, was 27 as compared with 25 for no. 19. A normal female sex chromatin pattern was found in oral mucosa cells. The parents had apparently normal chromosome complements in cells from blood cultures.

Case 102, a boy, showed a total chromosome count of 46 with a probable 21/21–22 translocation or isochromosome for the long arm of chromosome 21. Analyses of the chromosomes were based

[1] The relative length is the length of the chromosome relative to the total length of a haploid set containing the X chromosome, times 1000.

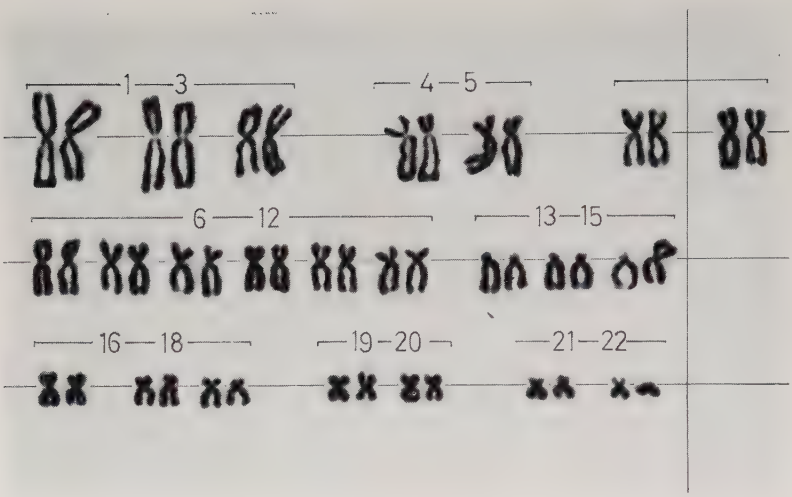


Fig. 10. Karyotype from a girl with Down's syndrome (Case 62). There are 46 chromosomes, including a presumptive 13–15/21 translocation.

on cells derived from blood, bone marrow and skin cultures. There were only three chromosomes in the 21–22 group but five chromosomes in the 19–20 group. The relative lengths[1] of the chromosomes were calculated from measurements of enlarged microphotographs of seven cells. The relative length of the extra chromosome, which was classified as the longest member of group 19–20, was 25 as compared 24 for no. 19. The patient was sex chromatin negative in cultured skin cells. Analyses of cultured leucocytes from the parents showed apparently normal karyotypes.

In each of these four patients with a presumptive 21/21–22 translocation or isochromosome 21 the relative length of the extra metacentric chromosome corresponded to double the length of the long arm of the chromosomes in group 21–22.

Case 62, a girl, showed a probable 13–15/21 translocation (Fig. 10). Analysis of the patient's chromosomes was based on cultured cells from peripheral blood and skin. The girl had 46 chromo-

[1] The relative length is the length of the chromosome relative to the total length of a haploid set containing the X chromosome, times 1000.

somes, but only four small acrocentric chromosomes were found instead of five as would have been expected in a female with Down's syndrome. There were only five chromosomes instead of six in the 13–15 group, but an additional submetacentric chromosome was found in the 6–12 group. This additional chromosome has probably originated through a reciprocal translocation between a chromosome 21 and one of the chromosomes in group 13–15. A normal female sex chromatin pattern was found in cultured skin cells. Analysis of cultured leucocytes and skin cells from the parents showed apparently normal karyotypes.

Other chromosome constitutions

Case 6, a girl, showed 46 chromosomes with an abnormal karyotype. This patient has previously been reported by Böök *et al.* (1961 *a*). Cytological observations based on one bone marrow and two skin biopsies taken from the right and left side of the body revealed a chromosome number of 46 and a consistent karyotype pattern (Fig. 11). In all cells there were five short acrocentric chromosomes of group 21–22, i.e. one additional chromosome. Satellites were never clearly visible on more than four of these five chromosomes. Ordinarily group 16–18 has six chromosomes, but in this case only five were observed. The odd chromosome was considered to be no. 16. A normal female sex chromatin pattern was found in oral mucosa and cultured skin cells. The karyotypes of the parents were apparently normal.

Case 52, a girl, was found to have 48 chromosomes. This patient will be reported in detail elsewhere (Gustavson and Lundström, in preparation). The chromosomal investigation of this patient was based on cell cultures derived from one skin and one bone marrow biopsy. One hundred and sixty-four cells were counted and 162 of them were found to have 48 chromosomes (Fig. 12). There was an extra chromosome in the 21–22 group. In addition, a satellited chromosome, which was smaller than the chromosomes in group 21–22, was found. This additional chromosome was metacentric and a region resembling a centromere was seen. Both arms of this chromosome resembled the satellite-bearing arms of

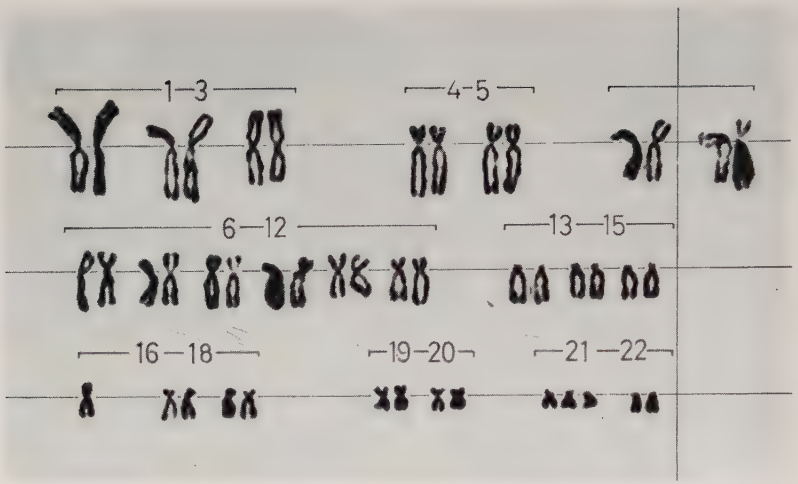


Fig. 11. Karyotype from Case 6, a mentally retarded girl. Only one chromosome number 16 is present, and there is an extra small acrocentric chromosome in group 21–22.

the acrocentrics. In about one-third of the cells satellites were observed on one arm of this small metacentric chromosome. Satellites were never observed on both arms of this chromosome. In two cells satellites were observed on all the five small acrocentrics and in two other cells all of the six large acrocentrics were satellited. Two of the cells counted were found to have 47 chromosomes. In one of these cells a chromosome 16 and in the other a small acrocentric chromosome was missing. The parents were found to have 46 chromosomes with apparently normal karyotypes in cultured cells from skin.

Sex chromatin

The sex chromatin was studied in cultured cells or in cells from buccal mucosa smears from 21 males and 24 females with Down's syndrome. All the affected males were sex chromatin negative. The females with Down's syndrome were all sex chromatin positive; the sex chromatin was of apparently normal size and the frequency of sex chromatin positive cells was within the range for normal females.

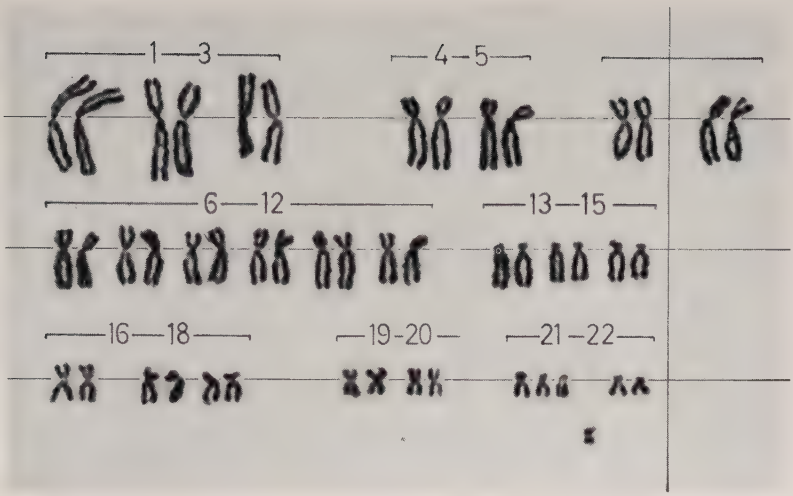


Fig. 12. Karyotype from a girl with Down's syndrome (Case 52). There are 48 chromosomes, including an extra chromosome in group 21–22 and an odd small satellited metacentric chromosome (placed below group 21–22).

Clinical Investigations

All clinical data have been summarized in Tables IV and V of the Appendix. In addition, short case reports comprising items of special interest are given in the Appendix.

Physical findings

Down's syndrome is characterized by a combination of mental deficiency and a varying number of more or less characteristic physical signs. In most cases a safe diagnosis can be made on clinical grounds. It must be emphasized, however, that there is no one strictly pathognomonic feature characteristic of Down's syndrome.

Diagnostic difficulties may occur at birth and during the first year of life, when some features of Down's syndrome, especially the mental retardation, are difficult or impossible to recognize (Carter and MacCarthy, 1951; Øster, 1951; Yannet, 1953; Lee *et al.*, 1961; Hall, in press).

One frequently accepted group of diagnostic characteristics is that of Øster (1953): "I have selected ten of the signs, which must—on a rough estimate—be regarded as 'characteristic' of mongolism, and which are known by experience to be rare in normals, and have called them 'cardinal signs'. These are: (1) four-finger line, (2) short crooked fifth finger, (3) short broad hands, (4) hyperflexibility, (5) oblique palpebral fissures, (6) epicanthus, (7) furrowed tongue, (8) irregular, abnormal sets of teeth, (9) narrow, high palate, and (10) flat occiput (brachycephaly). These signs are fairly age-stable, except furrowed tongue, which is not present in babies, and hyperflexibility as well as epicanthus, which are rare in old patients . . ."

"Taken as a whole we may say that mental defectives with four or more 'cardinal signs' in all probability are mongols."

Penrose (1949 *a*) states that "since the individual signs are not specific to the condition but may occur, though less frequently, in other types of cases and even in normal subjects, the diagnosis of mongolism is made by deliberately or unwittingly adding up the points in its favour".

I have personally examined 111 of the 119 individuals of the present series with Down's syndrome or suspected Down's syndrome. The physical examination was done with special regard to the physical signs generally ascribed to be associated with Down's syndrome (Øster, 1953; Carter and MacCarthy, 1951; Levinson *et al.*, 1955; Beckman *et al.*, 1962 *a*). In addition to Øster's 10 "cardinal signs" I have also recorded the presence or absence of the following traits: Brushfield spots, blepharitis, flat nasal bridge, permanently open mouth, protruding tongue, folded ears, gap between the 1st and 2nd toes, congenital heart defect and muscular hypotonia.

In this investigation a clinical diagnosis of Down's syndrome was accepted on the following grounds: mental retardation in combination with four or more of Øster's 10 cardinal signs. These diagnostic criteria were fulfilled by 93 of the 111 patients. These individuals had also, in addition to Øster's cardinal signs, other stigmata characteristic of Down's syndrome. The presence or ab-

TABLE 5. *Ninety-three individuals with a clinical and cytogenetical diagnosis of Down's syndrome distributed by number of positive signs according to Øster (1953) and positive signs used by the author (see the text).*

No. of positive signs	Øster's "10 cardinal signs" No. of signs available for observation: 10	9	21 signs used by the author No. of signs available for observation: 21	20
<4	—	—	—	—
4	5	5	—	—
5	8	4	—	—
6	18	9	1	—
7	18	4	—	1
8	13	1	3	1
9	7	—	3	2
10	1		5	2
11			6	3
12			10	6
13			11	3
14			12	3
15			8	1
16			6	1
17			4	—
18			1	—
19			—	—
20			—	—
21			—	
Total no. of ind.	70	23	70	23
No. of pos. signs per individual	6.7	6.3	12.9	11.7
Per cent ind. with at least:				
5 pos. signs	93±3.1 %	78±8.6 %	—	—
10 pos. signs	—	—	90±3.6 %	83±7.9 %

sence of the 21 signs used by the author and the 10 "cardinal signs" of Øster could be evaluated in 70 affected individuals of the current series. In this group each patient displayed on the average, 12.9 of the 21 signs used by the author. The observed

number of Øster's "cardinal signs" in this group was 6.7 per patient (see Table 5).

In 18 of the 111 cases examined by the author (Cases 6, 45, S 1–S 16) a diagnosis of Down's syndrome could not be made.

In the present series eight of the 119 cases (Cases 5, 9, 15, 23, 37, 74, 85 and 90) died before they could be examined by the author. However, these eight patients were all unquestionably affected with Down's syndrome according to their hospital records. They all had four or more of Øster's cardinal signs and, in addition, other stigmata characteristic of Down's syndrome.

Of the 101 patients of the present series who fulfilled the criteria for a clinical diagnosis of Down's syndrome, all had additional genetic material of chromosome 21, either in the form of trisomy, translocation, isochromosome or mosaicism.

Apparently normal karyotypes were found in 16 of the 18 patients who did not fulfil the criteria for a clinical diagnosis of Down's syndrome. Of these 16 individuals with normal karyotypes five had an apparently normal mental development which would rule out the possibility of Down's syndrome. Only two patients had more than two of Øster's 10 cardinal signs essential for a diagnosis of Down's syndrome. One of these two cases (Case S 1) was a boy with chondrodystrophia congenita punctata and normal mental development. Short stature, oblique palpebral fissures, a flat nasal bridge, protruding tongue and a Caffey's index typical of Down's syndrome, which were found in this boy, have been observed in other cases of chondrodystrophia congenita punctata (Allansmith and Senz, 1960; Rudhe, personal communication). The other patient (Case S 13), who had three of Øster's cardinal signs, probably had an atypical form of gargoylism.

Chromosomal aberrations were found in two of the 18 individuals in whom a diagnosis of Down's syndrome could not be made. One of these two patients (Case 6) had a probable deletion or translocation involving chromosome 16. Although this patient had some signs suggestive of Down's syndrome, others such as the general appearance and the dermal ridge patterns of the hands and feet contradicted this diagnosis.

TABLE 6. *Survey of the frequency of positive clinical findings.*

Clinical data	Cases with clinical and cytogenetical diagnoses of Down's syndrome			Cases with suspected Down's syndrome and normal karyotypes		
	No. of cases investigated	Investigated cases with positive findings		No. of cases investigated	Investigated cases with positive findings	
		no.	per cent		no.	per cent
Cephalic index, 83 and over	93	75	80.6	16	8	50.0
Oblique palpebral fissures	101	87	86.1	16	6	37.5
Epicanthic eye-fold	99	54	54.5	16	3	18.8
Blepharitis	94	43	45.7	16	1	6.3
Brushfield spots	95	66	69.5	16	2	12.5
Flat nasal bridge	99	61	61.6	16	8	50.0
Mouth permanently open	93	55	59.1	16	2	12.5
Abnormal size, shape and alignment of teeth	71	46	64.8	14	1	7.1
Protruding tongue	97	37	38.1	16	2	12.5
Furrowed tongue	94	41	43.6	16	—	—
High-arched palate	95	66	69.5	16	1	6.3
Narrow palate	94	71	75.5	16	1	6.3
Folded ear	93	26	28.0	16	—	—
Short and broad hands	99	74	74.7	16	—	—
Short 5th finger	100	74	74.0	16	5	31.3
Incurved 5th finger	98	51	52.0	16	6	37.5
Four-finger line	98	59	60.2	16	7	43.8
Gap between 1st and 2nd toes	95	83	87.4	16	6	37.5
Congenital heart defect	100	19	19.0	16	2	12.5
Hyperflexibility of joints	99	84	84.8	16	3	18.8
Muscular hypotonia	99	71	71.7	16	6	37.5
Abnormal middle phalanx of the 5th finger observed roentgenographically	53	34	64.2	11	1	9.1

The other patient (Case 45) was a girl with normal/21-trisomy mosaicism. Although she had some features suggestive of Down's syndrome, a diagnosis of that syndrome could not be made as her mental development was normal.

Table 6 gives the frequencies of the different clinical findings

Fig. 13. The foot of a child with Down's syndrome showing gap between the first and second toes and retroposition of the fourth toe.

in the sample of cases of Down's syndrome diagnosed both clinically and cytogenetically and in the sample of individuals with suspected Down's syndrome and normal karyotypes. Some of these signs noted in the patients with Down's syndrome have also been observed in mentally defective individuals but in a much lower frequency. A still lower rate of occurrence of some of the aforementioned signs has been reported in normal individuals (Øster, 1953; Böök and Fraccaro, 1956; Martin and Saller, 1957–1959; Beckman *et al.*, 1962 *a*). In the present series all the signs listed in Table 6 occurred more frequently in the group of patients with a clinical and cytological diagnosis of Down's syndrome than in the group of patients studied with normal karyotypes. The latter group had been investigated because of features suggestive of Down's syndrome. For almost all the signs tabulated in Table 6 the difference between the two groups was statistically significant.

In addition to the findings listed in Table 6 a number of other features might be mentioned. Thirty-one of 98 cases of Down's

syndrome as well as one of the cases with suspected Down's syndrome and a normal karyotype had umbilical hernias. In 13 per cent of cases affected with Down's syndrome there was only one flexion furrow of the 5th finger. Ten of the 93 cases of Down's syndrome examined by the author had syndactyly of the toes bilaterally. One of the 16 cases with suspected Down's syndrome and a normal karyotype (Case S 11) had syndactyly of the toes of the right foot. In no case did the syndactyly involve more than two toes. Six of the 93 cases of Down's syndrome had retroposition of the 4th toe bilaterally (Fig. 13) and one had bilateral retroposition of the 3rd toe. One of the 16 cases with suspected Down's syndrome and a normal karyotype (Case S 3) had retroposition of the 4th toes.

One of the cases with Down's syndrome and 21-trisomy (Case 79) had radioulnar synostosis, which is a common finding in the XXXXY-syndrome (Barr *et al.,* 1962).

Esophageal atresia was found in Case 5, duodenal atresia was present in Case 27 and anal atresia was noted in Case 94.

Case 80, a male with 21-trisomy and an XY sex chromosome constitution had, in addition to typical signs of Down's syndrome, features of Klinefelter's syndrome. Several sex chromatin negative male patients with clinical features in common with Klinefelter's syndrome have been karyotyped. These individuals had, as a rule, apparently normal karyotypes (Ferguson-Smith, 1963).

Body height

The body height was measured in 94 of the 101 cases of Down's syndrome in the present series (43 males and 51 females). These values are shown in Table IV of the Appendix. The body heights for males with Down's syndrome are plotted in the graph shown in Fig. 14, and for females with the same syndrome in the graph shown in Fig. 15. Because Case 31 had a marked gibbous deformity and Case 41 was a dwarf, the heights of these two individuals are excluded from the calculations and noted within brackets in Fig. 14. As observed in the graphs, only a few of the individuals with Down's syndrome have a normal height. The heights of

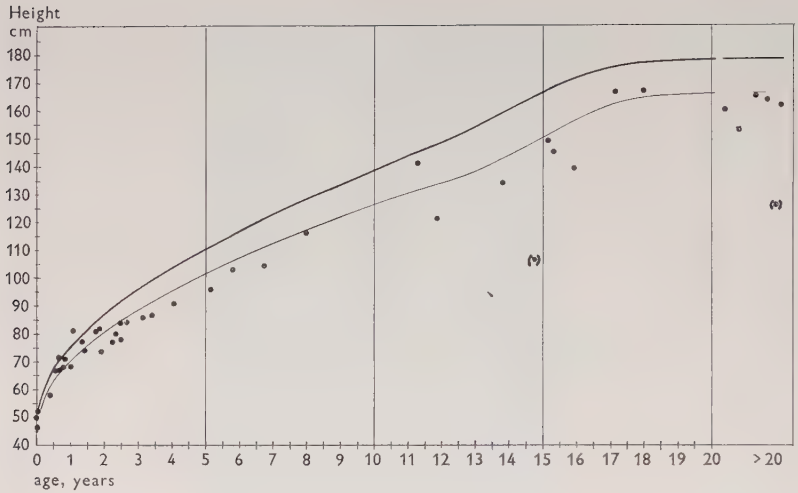


Fig. 14. Graph showing height in relation to age in 43 males with Down's syndrome. The heavy line denotes the mean height for normal males and the fine line the distance of two standard deviations below the mean height.

about 65 per cent of the cases of Down's syndrome are more than 2 standard deviations (S.D.) below the mean.

It is also seen that short stature becomes more marked with increasing age. As seen in the graphs (Figs. 14 and 15), it is not uncommon that the cases of Down's syndrome below two years of age have a height only slightly below the mean for normals of the same age. On the other hand, it is uncommon for the affected cases 15 years or older to have a body height close to the mean for normals of the same age. This is shown in the following table.

Age group, years	No. of individuals	Mean difference in height between affected individuals and normals in terms of the standard deviation (S.D.)
< 2	37	− 1.6 S.D.
2–14	30	− 2.4 S.D.
15 and over	25	− 3.1 S.D.

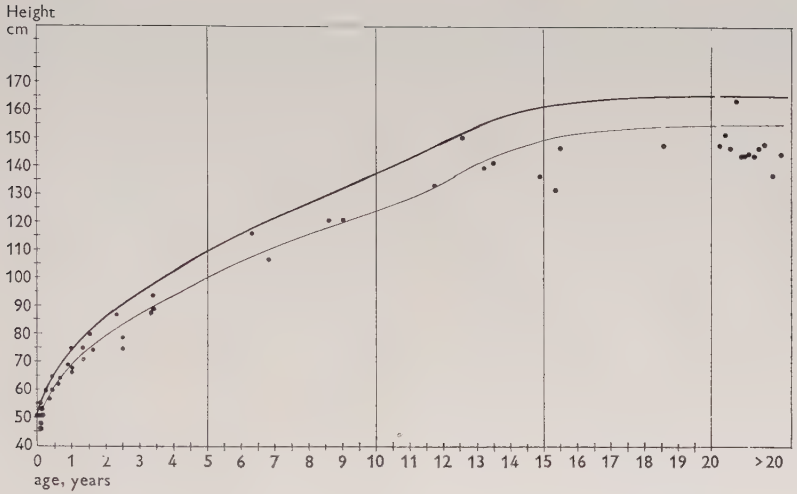


Fig. 15. Graph showing height in relation to age in 51 females with Down's syndrome. The heavy line denotes the mean height for normal females and the fine line the distance of two standard deviations below the mean height.

These findings indicate that the growth rate of the individuals with Down's syndrome in the present series is slower with increasing age compared to normals.

X-ray findings

The middle phalanx of the 5th finger was short and hypoplastic in 34 (64 per cent) of the 53 investigated cases of Down's syndrome of the present series (Appendix Table IV). In 19 of the 53 cases the middle phalanx of the 5th finger was normal. No instance of absence of the 5th middle phalanx was observed. The proportion of cases with an anomalous 5th middle phalanx is similar to that reported by Hefke (1940), who found a short middle phalanx in 62 of 100 cases of Down's syndrome. Stettner (1921) found a short middle phalanx of the 5th finger in 0.14 per cent of normal children. One of the individuals with suspected Down's syndrome and a normal karyotype (Case S 1) had a hypoplastic middle phalanx of the 5th finger.

TABLE 7. *Caffey's index in 46 individuals with clinical and cytological diagnoses of Down's syndrome and in five individuals with suspected Down's syndrome and a normal karyotype.*

These cases were less than one year of age at the time of X-ray examination.

Case no.	Sex	Age, months	Index	Case no.	Sex	Age, months	Index
			Individuals with Down's syndrome				
8	M	4.0	59	54	F	3.5	48
11	M	0.0	58	55	F	5.1	48
13	M	0.4	52	56	M	4.3	67
16	M	9.5	67	57	M	0.8	73
17	F	0.0	73	58	F	0.5	66
18	M	0.0	59	61	F	0.3	45
21	M	3.2	52	62	F	0.0	62
22	M	0.1	55	63	F	0.3	53
23	F	0.3	74	64	M	1.1	60
26	F	5.1	45	65	M	1.5	57
27	F	1.4	49	66	F	0.3	80
34	F	5.0	72	67	F	0.6	90
35	F	1.8	62	68	F	11.7	77
36	M	0.9	65	74	F	0.4	59
37	M	2.8	49	75	F	1.6	51
38	F	3.9	64	83	F	0.4	63
43	M	6.7	49	90	M	0.1	79
48	F	1.2	61	94	F	0.5	61
49	M	11.3	54	95	M	0.1	66
50	F	7.5	57	96	M	0.2	55
51	M	4.0	67	97	F	0.1	63
52	F	4.3	56	99	F	11.0	40
53	F	0.0	65	102	M	0.1	61
			Individuals with a normal karyotype (Suspected Down's syndrome)				
S1	M	0.1	52	S12	F	0.3	94
S3	M	3.9	73	S13	M	0.0	72
S4	F	0.8	68				

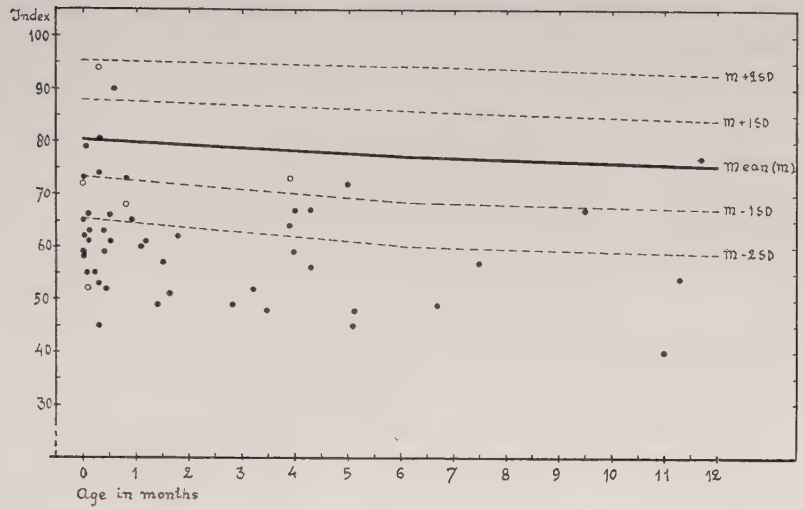


Fig. 16. Caffey's index in 46 individuals with clinical and cytological diagnoses of Down's syndrome (filled rings) and in five individuals with suspected Down's syndrome and a normal karyotype (open rings) plotted on the graph for normal distribution of Caffey's index (according to Caffey and Ross, 1958).

X-ray examination of the pelvis with calculation of Caffey's index was made in 46 cases of Down's syndrome below 12 months of age and in five cases of suspected Down's syndrome who were found to have apparently normal karyotypes (Table 7).

Caffey's index for each of these infants has been plotted on a graph showing the normal distribution (Fig. 16).

Only three of the 46 infants with Down's syndrome had a Caffey's index above the normal mean, four had an index between the normal mean and one standard deviation (S.D.) below the mean, eight had an index between the limits 1 and 2 S.D. below the mean, and 31 had a Caffey's index beyond 2 S.D. below the normal mean.

The overlap of the normal was thus confined to the lower half of the normal distribution with the exception of three infants who had values above the mean. Caffey's index for 31 (67 per cent) of the 46 infants with Down's syndrome was diagnostic, i.e. it lay

beyond 2 s.d. below the mean. One of the children with suspected Down's syndrome and a normal karyotype (Case S 1) had also a Caffey's index beyond 2 s.d. below the mean.

Pregnancy and neonatal data

Information was obtained regarding birth weight in 97, and duration of pregnancy in 93 of the patients with Down's syndrome. Information regarding birth height was obtained in 94 of the affected cases. One of these patients (Case 20), who was a twin, has been excluded from the calculations.

The mean heights at birth of females and males with Down's syndrome were significantly lower than those of control groups of 42,482 girls and 39,529 boys from the general Swedish population.[1] The mean height for females with Down's syndrome was 49.0 ± 0.3 cm and for affected males 48.3 ± 0.4 cm. The mean heights at birth in the control population were 50.5 cm for girls and 51.2 cm for boys. The difference in height between affected males and females was not statistically significant.

The mean birth weight of females with Down's syndrome was 3160 ± 90 g and of affected males 2920 ± 90 g. The difference in weight between affected males and females was not statistically significant. The mean birth weights in the control groups were 3440 g for girls and 3570 g for boys. The mean birth weights of females and males, respectively, with Down's syndrome were significantly lower than those of the control groups from the general Swedish population.

The low birth weights of children with Down's syndrome may be explained in part by early onset of labor. In the present series the mean duration of pregnancy was 269 ± 2.2 days for 42 males with Down's syndrome and 272 ± 2.0 days for 50 females with Down's syndrome. The mean duration of pregnancy of about 82,000 Swedish women was 280 days. The difference in duration

[1] Normal data from the general Swedish population on duration of pregnancy and on heights and weights at birth were kindly placed at my disposal by Associate Professor Lars Engström, Stockholm.

of pregnancy in women who gave birth to children with Down's syndrome and in women who gave birth to normal children is statistically significant.

In the present series, data on abortions and stillbirths in pregnancies prior to the birth of a child with Down's syndrome were obtained in 96 mothers. Of 147 pregnancies in this group 17 (11.6 ± 2.6 per cent) terminated in abortions and three (2.0 ± 1.2 per cent) resulted in stillbirths. The combined abortion and stillbirth rate was thus 13.6 ± 2.8 per cent. Øster (1953) found the combined abortion and stillbirth rate of the pregnancies occurring before the birth of children with Down's syndrome to be 9.7 ± 0.8 per cent in his Danish material. According to Øster "this hardly exceeds that in the general population". The difference in rate between the present series and Øster's material is not statistically significant. The frequency of spontaneous abortions in the general population is usually given as 10 per cent (Nilsson, 1957).

Maternal age at the time of birth of the patients with Down's syndrome

It is well known that there is an increased frequency of births of children with Down's syndrome with increasing maternal age (Penrose, 1933; Jenkins, 1933; Øster, 1953; Collman and Stoller, 1962) (See Table 1). The method of collecting cases of Down's syndrome in the present investigation cannot be expected to give a representative sample regarding the distribution of childbirths in relation to maternal age. Nevertheless it might be of interest to compare the distribution by maternal age, of births resulting in Down's syndrome, with that in a control population. The distribution of maternal ages at the time of birth of 92 nonfamilial cases of Down's syndrome in the present series compared with the distribution of maternal ages at birth in control material from the general Swedish population is shown in Table 8. The control sample consists of Swedish married women confined during the years which correspond to the birth years of the present series of individuals with Down's syndrome. The figures in columns 3 and

TABLE 8. *Mothers of 92 children with non-familial Down's syndrome distributed by age at birth of the affected child.*

Comparison between this distribution and the expected one obtained from Swedish official statistics (see the text).

Maternal age, years	Observed no. of mothers of 21-trisomy children	Expected no. of mothers of "normal" children (controls for 21-trisomy children)	Observed no. of mothers of translocation children	Expected no. of mothers of "normal" children (controls for translocation children)
<20	2	3.8	1	0.2
20–24	15	22.4	1	1.3
25–29	11[a]	26.8	1[b]	1.6
30–34	16	19.3	1	1.1
35–39	26	10.9	1	0.6
40 and over	17	3.8	—	0.2
Total no.	87	87.0	5	5.0

[a] One of these was the mother of a child who had an extra small metacentric chromosome in addition to 21-trisomy (Case 52).

[b] Mother of a child with 13–15/21 translocation. The four others were mothers of children with 21/21–22 translocation (or isochromosome for long arm of 21).

5 of Table 8 are based on over 3 million married women with live-born children. The mean age of the control material was 28.9 years.

The mean age of the mothers at birth of the 92 nonfamilial cases of Down's syndrome was 33.1 years. The mean age of the mothers at birth of the 87 nonfamilial cases with 21-trisomy was 33.4 years. Comparing columns 2 and 3 in Table 8 it is found that there is a significant overrepresentation of mothers 35 years old or older with 21-trisomy children ($P < 0.001$). The mean age of the mothers at birth of the five translocation cases was 27.5 years. The age distribution of mothers with translocation children (Table 8, col. 4) agrees with the age distribution of their normal controls (col. 5). The cases with a translocation are unfortunately too few to allow conclusions as regards the presence of an associa-

tion between the occurrence of the translocation cases and maternal age at their births.

The mean age of the mothers at birth of the nine familial cases of Down's syndrome was 31.5 years.

Diseases and defects in relatives of the patients

Many of the features seen in Down's syndrome, such as epicanthic eye-folds, fissured tongue, four-finger lines, brachycephaly and incurved short fifth-fingers are sometimes also found in normal individuals.

Some of the microsymptoms such as the four-finger line (Turpin and Lejeune, 1953) and fissured tongue (Turpin *et al.*, 1947) have been found to occur more frequently in family members of individuals with Down's syndrome than in the average population.

It has been shown from palm-prints of families containing one child or more with Down's syndrome that the affected children are more similar to their mothers than their fathers regarding the position of the axial triradius (Turpin and Lejeune, 1953; Penrose, 1954 *b*).

In the present series of 101 cases of Down's syndrome there are 4 cases with a family history of either clinodactyly or shortness of the 5th fingers (Case 21, 44, 52 and 68). In one case (Case 69) several close relatives have syndactyly of the 2nd and 3rd toes. However, no association between these traits and the presence of Down's syndrome in another member of the family can be proven from the data at hand.

An increased incidence of leukemia in patients with Down's syndrome has been demonstrated (Stewart *et al.*, 1958; Wald *et al.*, 1961; Holland *et al.*, 1962). In some families a tendency towards leukemia and to Down's syndrome or other conditions characterized by chromosomal anomalies has been reported (Buckton *et al.*, 1961; Miller *et al.*, 1961; Johnston, 1961; Baikie *et al.*, 1961; Thompson *et al.*, 1963; Miller, 1963).

In the present series one of the children with Down's syndrome (Case 11) developed acute leukemia. In three families a close relative of the child with Down's syndrome had died of acute leukemia.

Patients with Chromosomal Aberrations resembling those found in Down's Syndrome but with a Different Clinical Picture

The cytogenetical data are summarized in Appendix Table III.

Cases I and II were mentally defective female siblings, who had similar multiple congenital malformations. These patients have been described earlier (Gustavson *et al.*, 1962 *a*).

Family history and clinical findings

The father, born in 1919, and the mother, born in 1922, are both normal and healthy. A paternal great-grandfather had a hare lip and a maternal great aunt has had a disabling neurologic disorder since 20 years of age. A paternal cousin was born prematurely and has a cerebral palsy syndrome which is probably of prenatal origin.

The mother has been pregnant three times and has given birth to three living children. The first child, a daughter, born in 1948, is apparently normal and healthy. The second child, Case I, a female, was born in 1954 following an uncomplicated term pregnancy and delivery. Her birth weight was 2750 g. She was noted at the time of birth to have a cleft palate, micrognathia, two small preauricular papillomas on the left and a subluxation of the right hip. On subsequent hospitalizations the following additional findings have been observed: marked retardation in growth and in physical and mental development with idiocy and inability to talk, sit, stand or walk; underdeveloped musculature with hypotonia; microcephaly; strabismus; ptosis of the right eye; slight facial asymmetry; low-set, large, malformed ears; probable hearing impairment; and hyperflexibility of the fingers (Fig. 17). There was a tendency for the index finger to overlap the middle finger. No physical signs of heart disorder were found. The external genitalia were normal. At $7\,^1/_2$ years of age her height was 111 cm, her weight was 11.5 kg and her head circumference was 47.5 cm.

There have been repeated urinary infections, but no malformations were revealed at intravenous urography. Routine laboratory tests have otherwise been within normal limits. The dye test for toxoplasmosis and the Wassermann reaction were negative. Tests for phenylketonuria were negative. An EEG was normal. X-ray films of the skull showed microcephaly but no intracranial calcifications or other abnormalities.

The youngest sibling, a female, Case II, was born in 1956 following an uncomplicated term pregnancy and delivery. Her birth weight was 3000 g. The following anomalies were noted at birth: cleft palate;

Fig. 17. Case I at $7\,^1/_2$ years of age.

pronounced micrognathia; low-set malformed ears with an absent external auditory meatus on the right; probable hearing impairment; marked facial asymmetry; cartilage-containing papillomas anterior to both ears; rectal stenosis later confirmed by X-ray; and congenital heart defect. Subsequent examinations of Case II revealed marked retardation in growth and physical and mental development with idiocy and inability to talk, sit, stand or walk; underdeveloped musculature with hypotonia; microcephaly; strabismus; lacrimal duct stenosis; flexion of the fingers with tendency for the index finger to overlap the middle; and a nevus pigmentosus on the right cheek (Fig. 18). At $5\,^1/_2$ years of age her height

Fig. 18. Case II at $5\,^1/_2$ years of age.

was 99 cm, her weight was 10.5 kg and her head circumference was 46 cm. Routine laboratory tests were within normal limits. The dye test for toxoplasmosis, Wassermann reaction and urine phenylpyruvic test were negative. An EEG was normal. X-ray films showed microcephaly and the absence of the right mandibular ramus articularis and muscularis.

This patient developed pneumonia during the course of the present study and expired following a brief illness. Autopsy findings included an atrial septal defect of the secundum type. Gross examination of the brain revealed no abnormalities. The genito-urinary system was normal. Both ovaries appeared to be normal and no testicular tissue was found.

She and her sister were so similar in appearance and clinical findings that they appear to belong to the same syndrome.

Report on the main palmar lines and digital dermatoglyphics (Professor L. S. Penrose).

Case I (Fig. 19)

There are two features of interest. First, the distal triradius *t* on both hands is in a position commonly found in association with certain types of chromosome abnormality, in particular Down's syndrome and trisomy 13–15 (e.g. the sum of the maximal *atd* angles is 163° compared with 90° for control females and 143° for females with Down's syndrome in the same age group). The other point is a not very common extra triradius between *c* and *d*. In other respects, the hands are not characteristic of Down's syndrome, e.g. the radial loop on digit II and lack of pattern between *b* and *c* on the left hand.

Case II (Fig. 19)

The position of the *t* triradius is distal, as in many chromosomal anomalies. There is a hypothenar pattern. The arrangement of the

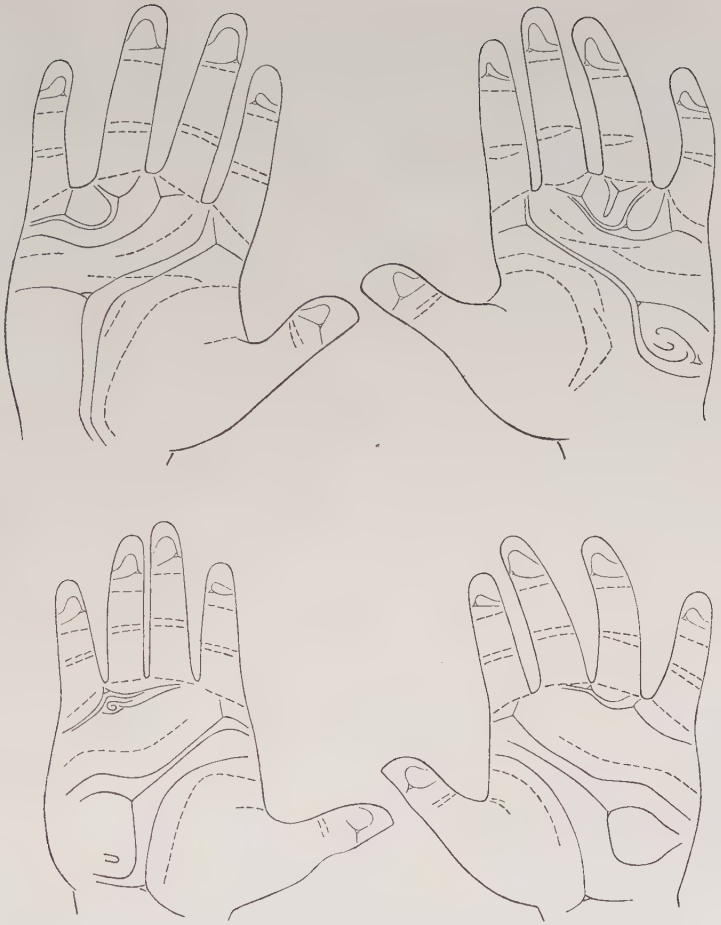


Fig. 19. Main lines of dermal ridges on palms of Case I (above) and Case II (below).

triradii, *a, b, c* and *d,* is very peculiar on both hands, probably *b* and *c* are both absent on the left hand. Again, the whole picture is not characteristic of Down's syndrome and there is a radial loop on digit II of the left hand.

Cytological studies

Analyses of chromosomes from the peripheral blood of both patients, the normal sibling and the parents were carried out.

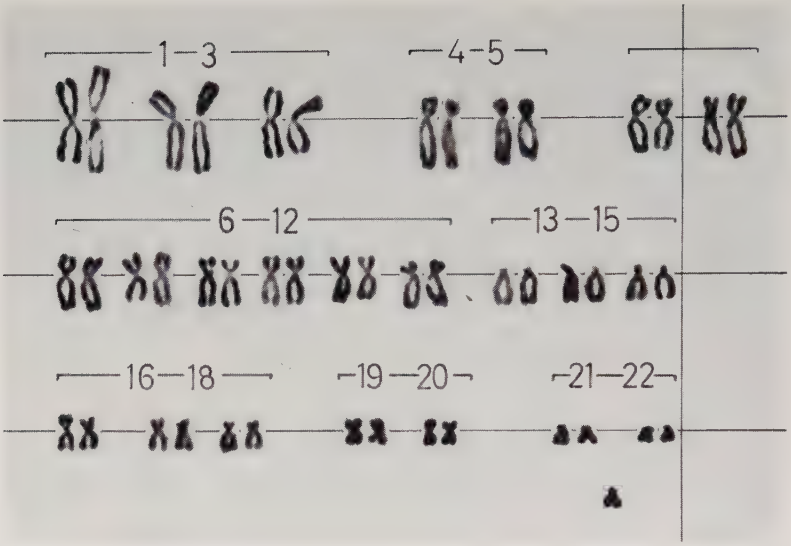


Fig. 20. Karyotype from Case I. There are 47 chromosomes, including an extra small chromosome placed below group 21–22.

Further chromosome analyses from Case II were based on the study of cell cultures derived from a skin biopsy one month prior to the death of the patient and of several tissues including brain, bone marrow, spleen, small intestine and gonads taken at the time of autopsy. The vast majority of analysable metaphase plates from cultures of tissues from Cases I and II had 47 chromosomes with an extra small acrocentric chromosome which had the same appearance in the karyotypes of both cases. A representative karyotype from each patient is shown in Figs. 20 and 21. This extra chromosome consistently looked larger than the other small acrocentrics. This difference was accounted for by slightly longer short arms (Fig. 22).

Satellites were never observed on this extra chromosome. Each patient showed a normal female sex chromatin pattern. Analyses of the cells from the normal sister and from both parents revealed apparently normal karyotypes.

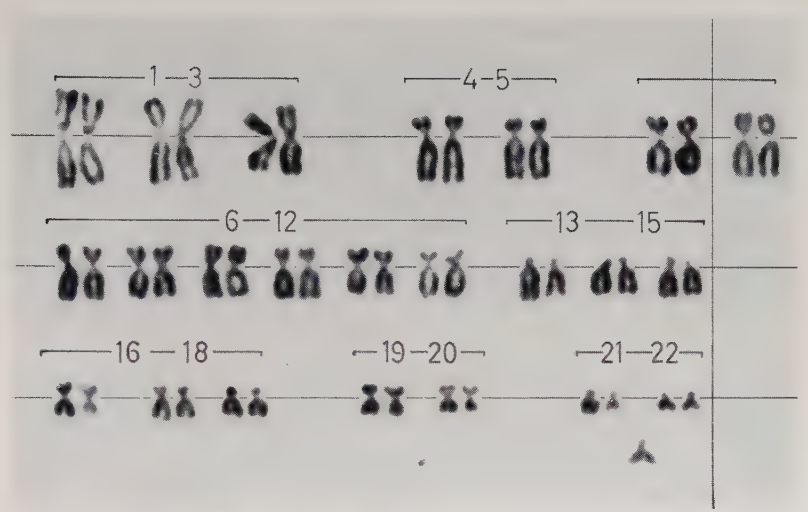
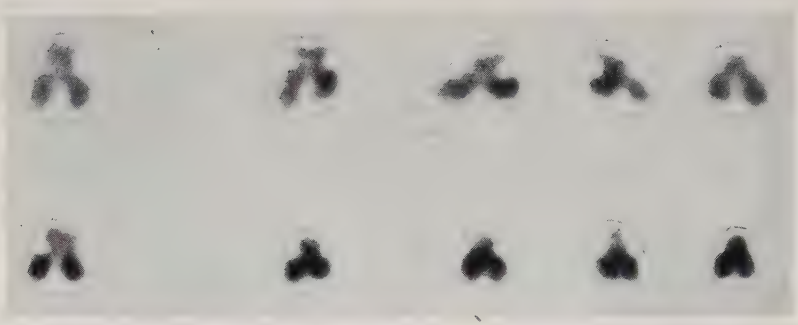


Fig. 21. Karyotype from Case II. There are 47 chromosomes, including an extra small chromosome placed below group 21–22.

Comments

These two siblings have very similar clinical and apparently identical cytological findings. The extra chromosome cannot be differentiated with certainty on cytomorphological grounds from the small acrocentric chromosomes. If the extra chromosome is interpreted as a part of a genuine trisomy in the group of small acrocentrics, the question arises whether it should be classified as a number 21 or 22. There were no features in the two siblings suggestive of Down's syndrome. Since by convention Down's syndrome is associated with trisomy for chromosome 21, the possibility of trisomy for chromosome 22 must be considered in Cases I and II.

A distinct clinical picture associated with trisomy for chromosome 22 has not been established. One patient with Sturge-Weber's syndrome (Hayward and Bower, 1960) was reported to have an extra small acrocentric chromosome. Reinvestigation of this patient showed, however, a karyotype "entirely consistent with XYY" (Dent *et al.*, 1963). Other investigated cases with



Case I.

Case II.

Fig. 22. The extra chromosome and the four short acrocentrics from two metaphase plates of Case I (above) and four metaphase plates of Case II (below).

Sturge-Weber's syndrome were found to have normal karyotypes (Lehmann and Forssman, 1960 *b*; Gustavson and Höök, 1961; Hall, 1961; Hayward and Bower, 1961).

Isolated cases with congenital hypotonia (Dunn *et al.*, 1961;

Zellweger *et al.*, 1962 *a*) and childhood schizophrenia (Turner and Jennings, 1961; Biesele *et al.*, 1962 *b*), a mentally retarded girl with congenital cataract, hearing defect and muscular hypotonia (Zellweger *et al.*, 1962 *a*), a girl with retarded development, congenital heart disease and muscular hypotonia (Koulischer and Perier, 1962), a boy with a cavernous hemangioma (Beçak *et al.*, 1963), a boy with punctate epiphyseal dysplasia (Haylock and Williams, 1963) have been reported to have an extra acrocentric chromosome which could possibly be a number 22. An extra small acrocentric chromosome has been found in a proportion of cells of persons with dystrophia myotonica (Fitzgerald, 1962).

The two patients reported here do not resemble any of these cases.

The extra chromosome of Cases I and II did not have the morphological properties of a Y chromosome. That the extra chromosome is a Y chromosome seems also unlikely as both of the patients had normal female genitalia and later Case II was shown at autopsy to have a normal female genital tract.

The extra chromosome could be the result of structural rearrangements. The morphological characteristics make it possible, for example, that it is an 18 with a partial deletion of the long arm. Therefore, it is of interest to compare the clinical findings of the present patients with those in the cases reported to have a trisomy for 17 or 18 (Smith, 1963). Cases I and II have in common with trisomy 17–18 the following characteristics: mental deficiency, micrognathia, flexion of the fingers, and low-set malformed ears. Case II also had an atrial septal defect of the secundum type; 14 out of 17 previously reported patients with 17 or 18-trisomy also had a congenital heart defect, usually an interventricular septal defect. Whereas a renal anomaly has been common in this syndrome, it has not been demonstrated in the affected sisters through clinical study in both and post-mortem examination in one. Cleft palate, which has been rare in other cases, was present in both the patients.

Assuming the extra chromosome in these two patients to be a deleted 18, it is interesting to speculate that the difference between

their clinical picture and that of patients with trisomy 17–18 might be due at least partly to the loss of part of the long arm of the extra chromosome. A patient with features similar to those of trisomy 17–18 was reported by Crawfurd (1961) to have an extra 17–18 with a partial deletion of the long arm, but this patient differed in several respects from the present cases.

Mental retardation, hearing impairment, cleft palate and malformed ears are found in the majority of patients with trisomy 13–15 as well as in the present cases (Smith, 1963). The present cases lack several features, however, which are usually associated with a trisomy in the 13–15 group: seizures, hemangiomas, microphthalmia, hare lip and polydactyly.

A girl with a supernumerary small acrocentric chromosome and with clinical findings similar to those of the present cases was reported by Zellweger *et al.* (1962 *b*). Their patient was regarded as having a partial D-trisomy syndrome. A mentally retarded boy investigated in this laboratory (Böök and Santesson, personal communication), a mentally retarded boy published by Hall (1963 *a*) and a mentally retarded boy reported by Ferguson and Pitt (1963) each had an extra small acrocentric chromosome. The clinical findings of these three patients were strikingly similar to the two sisters under discussion.

The fact that the parents of the present cases showed a normal karyotype makes it possible that the event leading to the chromosomal abnormality in the two sisters occurred in a premeiotic cell division in one of the parental gonads. A resulting stem-line with cells containing 47 chromosomes could then have produced both gametes with 24 chromosomes including the extra chromosome and gametes with a normal haploid set. If the extra chromosome is a no. 22 one must also assume nondisjunction in each case as a possible cause of the extra chromosome.

Case III, previously reported by Gustavson *et al.,* 1962 *b,* was a newborn boy with multiple malformations of the type usually seen in the (13–15)-trisomy syndrome (Patau *et al.,* 1960). Chromosomal analyses showed a probable (13–15)-trisomy and, in addition, an extra chromosome in the group of small acrocentrics.

Family history and clinical findings

The mother, born in 1936, and the father, born in 1935, were both healthy. Down's syndrome, gross malformations, significant mental retardation, or other congenital defects were not known to have occurred among the relatives. The first pregnancy resulted, after seven months gestation, in the birth of a boy. His birth weight was 1150 g and he survived for only 8 hours. At autopsy the cause of death was found to be a cerebral intraventricular hemorrhage. No malformations were recorded.

The second child, a boy, who is the subject of this investigation, was born 10 days after the expected date of confinement. The delivery was normal. The birth weight was 2460 g, the height 45 cm and the head circumference 32 cm. The orbits and the eyeballs were quite small. An ulceration, measuring 2×3 cm, was observed over the anterior fontanel. His ears were low-set but of normal appearance. He had small 6th digits on the ulnar side of both hands. There were no physical signs of congenital heart disease and the ECG was normal. Abdominal examination revealed a supra-umbilical hernia, 1.5 cm in diameter. There were no signs of Down's syndrome present such as epicanthic eye-fold, oblique palpebral fissures, brachycephaly, increased skin folds of the back of the neck or clinodactyly. Signs of postmaturity such as meconium staining, dry and scaly skin or abnormally long finger nails were not observed. Apnea occurred immediately after birth and lasted for about 8 minutes until respiration could be initiated with the aid of intubation. He had several attacks of cyanosis and died about 34 hours later, after a generalized convulsive seizure.

The autopsy showed multiple malformations including microphthalmia, polydactyly, and cardiac ventricular septal defect. There was increased venous vascularization of the leptomeninges bilaterally. The kidneys, liver and pancreas were dysplastic with an excess of thinwalled blood vessels. An excessive vascularity of the lungs and, to a lesser degree of the myocardium was found.

Cytological observations

Chromosome studies were carried out on cultures of bone marrow obtained from two ribs. Primary cultures and several subcultures of both specimens were used for chromosome counts and karyotype analyses. Sixty-five apparently undamaged cells in mitotic metaphase were analysed. Sixty-four of these cells were found to have forty-eight chromosomes.

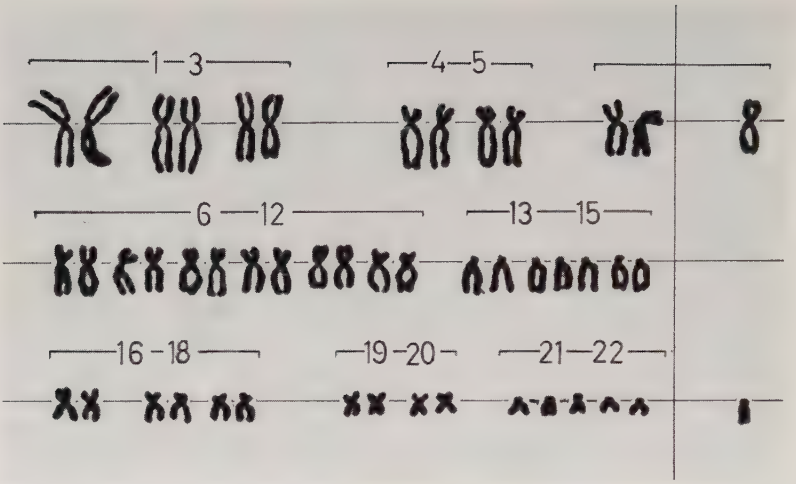


Fig. 23. Karyotype from Case III. There are 48 chromosomes, including one extra chromosome in the 13–15 group and one extra chromosome in the 21–22-Y group.

Seventeen cells with 48 chromosomes were subjected to a detailed analysis by inspection in the microscope and with the aid of enlarged photomicrographs. Seven large and six small acrocentric chromosomes were found in each of these cells (Fig. 23). In one cell which had not been treated with colchicine, satellites were observed on all of the seven large acrocentrics. From the appearance of the six small acrocentrics it was not possible to identify the extra chromosome in this group, i.e. to decide whether it could be a second Y chromosome or an extra autosome of the 21–22 group. Satellites were never clearly visible on more than three of these chromosomes, neither could these small acrocentrics be classified as (21–22) autosomes or Y chromosomes by other morphological criteria.

Blood cultures from the parents showed apparently normal karyotypes.

Comments

The coexistence of double chromosomal trisomy is rare. In 1961 Gagnon *et al.* reported a child with double trisomy involving chromosomes 18 and 21. The clinical pattern seemed to be a mixture of Down's syndrome and the (17–18)-trisomy syndrome, the latter being more apparent. 18-trisomy has also been observed in association with a triple X sex chromosome constitution (Uchida *et al.,* 1962).

The combination of trisomy for chromosome 21 and an XXX sex chromosome constitution has been found in a girl with retinoblastoma (Day *et al.,* 1963).

A girl with a combination of the manifestations of Down's syndrome and of the (13–15)-trisomy syndrome was found to have (13–15)-trisomy and 21-trisomy (Becker *et al.,* 1963).

The present case shows many of the structural anomalies described in previous examples of (13–15)-trisomy (Smith, 1963). The cytological data confirmed a trisomy in the group of large acrocentrics (13–15). No attempt was made to classify the extra chromosome according to a particular chromosome pair within this group, as it is generally agreed that the three pairs of large acrocentrics are indistinguishable on the basis of their morphological appearance in mitotic metaphases. Assuming that the other extra chromosome belongs to the group of small acrocentric autosomes it could be either a 21 or a 22. As there were no signs or symptoms of Down's syndrome, 21-trisomy appears rather unlikely. A specific syndrome associated with trisomy for chromosome 22 is at present not known. The extra small chromosome may be the result of structural rearrangements, e.g. a deleted large acrocentric chromosome.

The extra small chromosome may be a Y chromosome. The existing reports of individuals with an extra Y chromosome do not suggest any gross phenotypical effect caused by this additional chromosome. Two of these patients have been reported to have an XXYY sex chromosome constitution and both were phenotypically similar to the XXY Klinefelter syndrome (Muldal and Ockey, 1960; Ellis *et al.,* 1961). The only individual reported to

have simply an extra Y chromosome was a normal male (Sandberg *et al.*, 1961).

All of the small acrocentrics in the cells of the present case were about equal in length and in the majority of cells identification of the Y chromosome by its morphological features was impossible.

The extra chromosomes in this case could have arisen in several ways:

(1) Assuming that the extra small chromosome is a 21 or 22 it could have resulted from maternal or paternal nondisjunction.
(2) Assuming that the extra small chromosome is a Y, it could have resulted from nondisjunction of the Y during the second meiotic division.
(3) The extra large acrocentric chromosome could have resulted from maternal or paternal nondisjunction in the 13–15 group during meiosis.
(4) Either one or both of the extra chromosomes could have arisen as a result of mitotic nondisjunction.

Case IV, to be reported in detail elsewhere (Gustavson *et al.*, 1964 *a*), is a male infant with multiple congenital anomalies including hypotonia, retarded growth and development, marked hydrocephalus, low-set malformed ears, micrognathia, macroglossia, omphalocele, absence of one umbilical artery, malrotation of the small intestine, anal atresia, and moderate hydronephrosis. Chromosomal investigation showed 46 chromosomes including a probable 4–5/21–22 translocation. The maternal grandfather and mother were found to be carriers of the same translocation.

Family history

At the time of the patient's birth, his mother was 33 and his father was 37 years of age. Both parents were normal and in good health. The mother, who was the last of four siblings, was born when her mother was 38 and her father 36 years old. The father of Case IV was the first of two siblings. No cases of malformation or mental retardation had been recorded among near relatives with the single exception that the mother had a severely mentally retarded brother who had died at

the age of 21 in a mental institution. This uncle of the patient had short stature and a big protruding tongue but no other known malformations.

The mother of Case IV had had a total of five pregnancies. Her first pregnancy in 1954 resulted in the delivery of an apparently normal male who died in the perinatal period. Her second pregnancy in 1956 resulted in the delivery of a normal male who is now alive and healthy. She had two abortions in 1960 at the second and third months of gestation, respectively. The present case is the product of her fifth pregnancy. She had an uncomplicated prenatal course with the present child until the onset of vaginal bleeding one day before delivery. She had no past history of serious illnesses.

Clinical findings

Case IV was delivered three weeks prematurely by Cesarean section performed because of maternal vaginal bleeding which began the previous day. His birth weight was 3300 g and his length was 50 cm. It was noted that the umbilical cord contained only one umbilical artery. Because of an omphalocele and anal atresia the child was immediately transferred to a pediatric surgery department. He had marked micrognathia with macroglossia.

The child had surgical repair of the omphalocele and anal atresia on the day of birth. The omphalocele was described as being egg-sized and the pedicle was 1.5 cm in diameter. A portion of the small intestine was incarcerated and discolored inside the omphalocele. Only one umbilical artery, the right, was found. A marked diastasis recti was observed. The anal atresia was of the membranous type. The external genitalia were normal.

At 11 days of age the child (Fig. 24) was transferred to the medical department. Physical examination revealed the following significant features in addition to those already described:

Scaphocephaly with premature synostosis of the sagittal suture; anterior fontanel (3 × 3 cm) with normal tension; pronounced micrognathia; a high-arched palate; macroglossia; slight hypertelorism; very small palpebral openings; absence of epicanthic folds; and low-set malformed ears with folding-over of the upper border of the helix so that the upper margin formed a right angle with the descending part of the helix. There was mild scoliosis in the lumbar region. The thoracic cage was soft with respiratory retractions, but ausculatory findings of the chest were normal. There was no hepato-splenomegaly. The fingers and toes were unusually long and there was a distinct gap between the first and second toes. There was no four-finger line.

Neurological examination showed generalized hypotonia with hypo-

Fig. 24. Case IV at 11 days of age.

active Moro reflex and deep tendon reflexes. The stepping and walking reflexes were slow.

Ophthalmological examination revealed blepharophimosis and colobomata of the irides on the nasal side in the lower half of each eye. The eye grounds were normal centrally but were not visualized peripherally.

The head circumference, which measured 37 cm at birth, increased to 46 cm at two months of age, and at the time of death, when the patient was 3 1/2 months old, the head circumference measured 59 cm.

A bone marrow aspirate was obtained after immature, atypical, vacuolated mononuclear cells were noticed in the peripheral blood. The

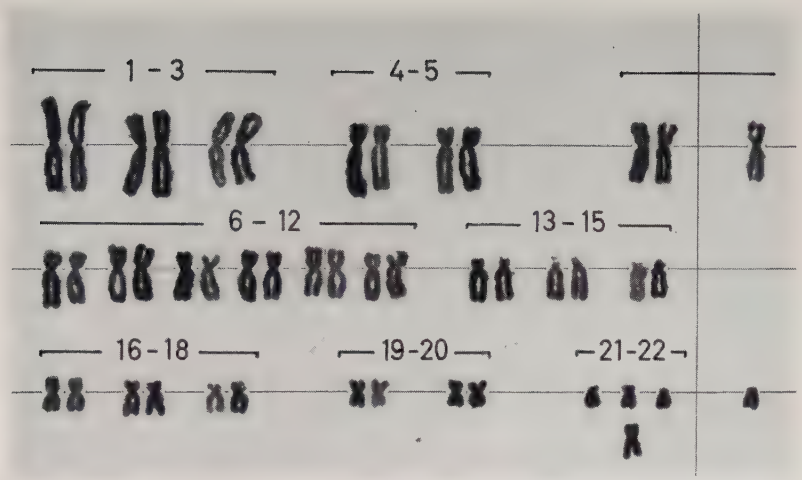


Fig. 25. Karyotype from Case IV. There are only three chromosomes in the 21–22 group and there is one unpaired chromosome (placed below group 21–22) with submedian centromere.

marrow contained a large number of vacuolated mononuclear cells but was otherwise normal.

An X-ray film of the skull and a pneumoencephalogram showed synostosis of the sagittal suture and marked dilatation of the ventricular system. Other radiographic examinations showed the presence of a hiatus hernia, malrotation of the small intestine, and dilatation of the left renal pelvis. An EEG was normal. The cerebrospinal fluid was normal. The hemoglobin was 15.9 g/100 ml. The white blood cell count varied between 15,000 and 42,000 per cmm. The platelets varied between 480,000 and 990,000 per cmm. The urinary sediment was normal, but there was slight proteinuria. Tests for phenylketonuria were negative. The child's general condition remained poor and he died at 3 1/2 months of age.

Cytological studies

The analysis of the patient's chromosomes was based on the study of cell cultures derived from one bone marrow and two skin biopsies. The karyotype contained only four small acrocentrics and one chromosome which could not be matched. This odd chromosome was metacentric. In most of the plates one of the

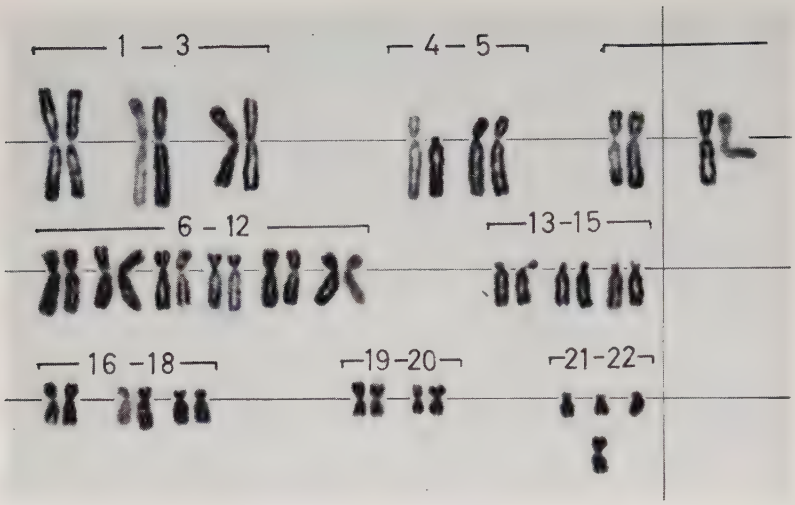


Fig. 26. Karyotype from the mother of Case IV. The short arm of a member of group 4–5 is missing, and a member of group 21–22 is absent. An unpaired chromosome similar to that found in the index case is present.

small acrocentric chromosomes was identified as a Y chromosome because of straight chromatids. The relative length[1] of each chromosome was calculated from measurements of enlarged photomicrographs of 8 cells. The relative length of the odd metacentric chromosome was 25 as compared with 25 for no. 19 and 27 for no. 18. The number of satellited small chromosomes never exceeded 3 in any of the preparations. The karyotype is shown in Fig. 25. The karyotype was similar to that described in cases of Down's syndrome with a 21/21–22 type of translocation.

Chromosome studies on the parents were carried out on cultures derived from skin biopsies. Analysis of cells derived from the mother showed a chromosome number of 46. There were only three small acrocentric chromosomes. In addition to the same unusual chromosome present in the karyotype of her son, one of the chromosomes in group 4–5 lacked the short arm (Fig. 26).

[1] The relative length is the length of the chromosome relative to the total length of a haploid set containing the X chromosome, times 1000.

The maternal grandfather was found to be a carrier of the same translocation. The karyotype of the father was normal.

The most likely interpretation of the chromosome abnormality in the mother and the maternal grandfather is a reciprocal translocation involving a chromosome of group 4–5 and a member of group 21–22. The translocation chromosome was transmitted from the maternal grandfather through the mother to her son. The maternal grandfather and the mother are carriers of the translocation chromosome and their chromosome complements are balanced. The son was effectively trisomic for the short arm of a chromosome 4 or 5.

Comments

The presumptive translocation found in the present family is probably reciprocal. Theoretically an individual heterozygous for a reciprocal translocation can produce many kinds of gametes. The behaviour of reciprocal translocations in plants (Darlington, 1937) and the mouse (Carter *et al.*, 1956) indicates that the gametic output consists mainly of four types. In the family under discussion these four types of gametes produced by the mother and the corresponding zygotes resulting after fertilization with a normal sperm are illustrated in Fig. 27. The first type of gamete shows the translocation chromosome and a normal chromosome no. 4 or 5. The zygote formed by the union of this gamete and a normal male gamete has the same chromosome constitution as the index patient, who is effectively trisomic for most of the short arm of no. 4 or 5. The second type of gamete is normal. The third type of gamete contains a chromosome no. 4 or 5 with loss of most of the short arm and the translocation chromosome. The zygote formed by the union of this gamete and a normal male gamete would have the same karyotype as the mother, and would probably develop into a phenotypically normal individual. This individual would, however, again produce gametes of the same four types. The fourth type of gamete shows a chromosome no. 4 or 5 with loss of most of its short arm and a normal chromosome 21. The corresponding zygote resulting from the union with a normal

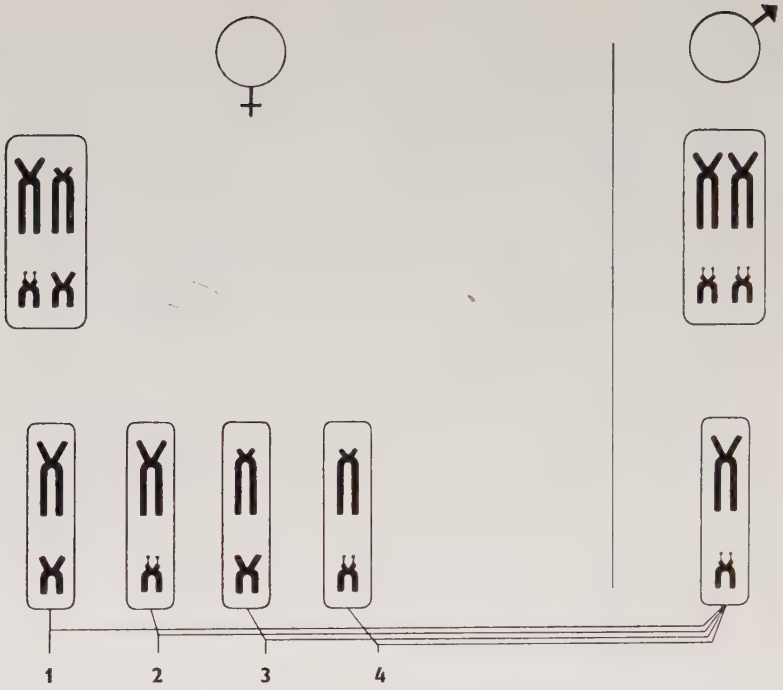


Fig. 27. Schematic drawing showing the four main types of zygotes resulting from the mating between a normal father and a mother who is a carrier of a translocation chromosome of the type found in Case IV. 1, Trisomy for most of the short arm of no. 4 or 5 (the index case); 2, Normal; 3, Balanced carrier; 4, Monosomy for most of the short arm of no. 4 or 5.

male gamete would be monosomic for most of the short arm of a chromosome 4 or 5. Such individuals have been described by Böök *et al.* (1963) and Lejeune *et al.* (1963 *b*).

Some cases not having Down's syndrome and with multiple congenital malformations associated with translocations have been reported (Brodie and Dallaire, 1962; Edwards *et al.*, 1962; Vieslie *et al.*, 1962; Gagnon *et al.*, 1963; Hecht *et al.*, 1963 *a*; Jacobsen *et al.*, 1963; de Lozzio and Valencia, 1963).

It is possible that, in the family under discussion, the two embryos lost by miscarriages were chromosomally unbalanced.

Some mothers who are heterozygous for a 13–15/21 translocation and have produced children with Down's syndrome carrying this translocation seem to have a high frequency of miscarriages (Penrose and Delhanty, 1961; German *et al.*, 1962 *a*; MacIntyre *et al.*, 1962).

Abnormalities in growth and development of about the same severity as found in this patient are also seen in the (13–15)-trisomy syndrome and the (17–18)-trisomy syndrome.

None of the three established autosomal syndromes, that is, 21-trisomy, (13–15)-trisomy or (17–18)-trisomy have the malformation syndrome of this case although some of the features of the present case are a common finding in them. Muscular hypotonia, malformed ears, colobomata of the irides and small palpebral openings are common findings in the (13–15)-trisomy syndrome, and micrognathia, a high-arched palate, low-set, malformed ears, renal anomaly and unusually long fingers in the (17–18)-trisomy syndrome. Muscular hypotonia, macroglossia, a high-arched palate, ears with angular, folded upper helix and a distinct gap between the first and second toes which are common findings in Down's syndrome were also found in this patient.

The finding in the present case of a missing umbilical artery is interesting because of the association between absence of one umbilical artery and malformations (Bourne and Benirschke, 1960; Faierman, 1960). The abnormalities in the cases with an absent umbilical artery are mostly multiple. In these cases obstructive lesions or atresia of the gastrointestinal and urinary tracts are common. Absence of one umbilical artery has been found in cases of (17–18)-trisomy (German *et al.*, 1962 *b*; Lewis, 1962), in (13–15)-trisomy (Miller *et al.*, 1962), and in Down's syndrome (Case 37 of the present series).

DISCUSSION

In the present study 119 individuals with Down's syndrome or suspected Down's syndrome were karyotyped. Ninety-four of these cases were trisomic for chromosome 21 and two showed mosaicism involving chromosome 21. One of the mosaics was of the type normal/trisomy 21, the other of the type normal/trisomy 21/trisomy 21 plus isochromosome 21. No evidence of mosaicism involving chromosome 21 was found in the remaining 117 cases. However, some of these might have had mosaicism which escaped detection. Four of the patients had a presumptive 21/21–22 translocation or alternatively a presumptive isochromosome for the long arm of chromosome 21, and one patient had a probable 13–15/21 translocation. Another patient had 48 chromosomes, including an extra small acrocentric chromosome and a small satellited metacentric chromosome. One of the cases of suspected Down's syndrome had a probable deletion or translocation involving chromosome 16. Sixteen of the 57 cases with suspected Down's syndrome had an apparently normal karyotype.

The criteria for the clinical diagnosis of Down's syndrome were mental retardation and four or more of Øster's 10 "cardinal signs" (Øster, 1953) (see p. 62).

Of the 119 cases in the present series 101 were found to fulfil the above criteria for a clinical diagnosis of Down's syndrome. These 101 cases of Down's syndrome all had extra genetic material of chromosome 21, either in the form of trisomy, translocation, isochromosome or mosaicism.

All patients with Down's syndrome whose karyotypes have so far been reported, with one exception, have had extra genetic material of chromosome 21. The exception is a boy, claimed to be a case of Down's syndrome with a normal chromosome constitution (Hall, 1962).

In the present series the 16 individuals with normal karyotypes, the mosaic of type normal/trisomy 21 (Case 45) and the patient with a probable deletion or translocation involving chromosome 16 (Case 6) did not fulfil the criteria for a clinical diagnosis of Down's syndrome when examined by the author.

Nonfamilial Cases of Down's Syndrome

Among the 101 patients with Down's syndrome 92 had no close relative with this disease. The majority (93 per cent) of these 92 patients had 21-trisomy and only 6 (7 per cent) showed a karyotype different from the usual 21-trisomy. That 21-trisomy is by far the most common chromosome anomaly in nonfamilial cases of Down's syndrome is in agreement with the findings of Hyashi (1963) who karyotyped 77 isolated cases of Down's syndrome and found that 72 (94 per cent) of these patients were trisomic for chromosome 21. Other investigations also indicate that the most frequent chromosome anomaly in Down's syndrome is 21-trisomy (Lejeune, 1960; Makino *et al.,* 1960; Böök, 1961; Breg *et al.,* 1962 *a*; Hamerton, 1962; Lehman *et al.,* 1962).

Five of the 92 isolated cases of Down's syndrome in the present study showed a presumptive translocation or isochromosome involving chromosome 21. Hyashi (1963) found that three of his 77 isolated cases of Down's syndrome had a translocation chromosome.

A striking increase in the relative frequency of birth of children with Down's syndrome is known to occur with increasing maternal age (Penrose, 1934, 1961 *a*; Øster, 1953; Collman and Stoller, 1962). This was also observed in the present material (Table 8). A maternal age effect has also been reported in Klinefelter's syndrome (Lenz *et al.,* 1959) in the 17–18 and in the 13–15 trisomy syndrome (Hecht *et al.,* 1963 *b*; Lejeune, 1963). There is also some evidence in Drosophila that aging might dispose to nondisjunction (Brown and Hannah, 1952; Hannah, 1955).

That the incidence of nondisjunction probably increases with increasing maternal age suggests an aging effect on those oocytes

that are shed late in the fertile period (c.f. Hamerton, 1962; Hall, 1963 *a*). The mechanism of this aging effect is unknown.

However, the possibility that influences causing nondisjunction in early embryonic divisions might increase with increasing maternal age is not excluded.

It has been suggested that nondisjunction might also take place during meiosis in males, but that a selective mechanism might be operating against unbalanced sperms, though not against unbalanced ova with an extra chromosome 21 (Penrose, 1962).

According to Penrose (1951, 1961 *a*) and Collman and Stoller (1962) the distribution of maternal ages at birth of children with Down's syndrome is bimodal with a minor peak at the average maternal age for normal controls and a major peak at a maternal age above 40 years. This suggests that for some cases of Down's syndrome mechanisms independent of maternal age are etiologically important. These mechanisms may include: (1) Translocations (or isochromosomes) produced during gametogenesis in a parent or inherited from a parent carrying the translocation (or isochromosome). (2) Trisomy 21 following secondary nondisjunction during gametogenesis in a parent with 21-trisomy in at least a part of the gonad. (3) Nondisjunction facilitated by genetic or environmental factors.

Genes causing abnormal chromosome behavior have been found in several organisms, e.g. in maize (Beadle, 1933). A recessive gene in *Drosophila simulans* is, when homozygous, associated with nondisjunction in the female (Wald, 1936). In human pedigrees a similar mechanism associated with nondisjunction might be suspected if parents of mothers of trisomics were frequently consanguineous. In the latter case it is possible that the mother of the trisomic child could have a homozygous recessive gene which might in some way cause nondisjunction during oogenesis (Penrose, 1961 *a*). In the present series of Down's syndrome and suspected Down's syndrome none of the parents were cousins and none of the parents were known to have cousin parents.

Structural changes are known to favor abnormal segregation during meiosis of the chromosomes involved in the change. For

example, abnormal segregation of chromosome 21 during meiosis in female carriers of a presumptive 21/13–15 translocation is reported. An inversion within a chromosome 21 could inhibit synapsis in meiotic prophase and both chromosomes may migrate to the same pole. Inversions may, however, not be recognizable in somatic cells unless they involve centromeres and cause a change in the arm ratio. In Drosophila autosomal structural rearrangements have been found to cause abnormal segregation of the Y chromosome (Grell, 1959).

Four of the 92 isolated cases of Down's syndrome in the present series showed 46 chromosomes and a karyotype which morphologically could be interpreted as the result of a 21/21 translocation, a 21/22 translocation, or an isochromosome for the long arm of chromosome 21. There is, however, no real evidence as to which type of rearrangements these chromosomes demonstrate as no convincing meiotic studies so far have been done.

In each of these four cases the odd metacentric chromosome resembled a member of group 19–20 (Fig. 9). One of the fathers of these children was unknown, hence his karyotype could not be determined. Otherwise, the karyotypes of the parents of these four children were apparently normal. A presumptive translocation of the 21/21–22 type or a presumptive isochromosome 21 could have been formed during gametogenesis in one of the parents. The fertilization of an unbalanced gamete carrying this abnormal chromosome would result in a zygote with Down's syndrome.

Isochromosomes are considered to be the result of misdivision of the centromeres during meiosis (Darlington, 1939; Sears, 1952; Lindsten *et al.*, 1963). Misdivision of the centromere and formation of an isochromosome might also occur during mitosis. The formation of an isochromosome for the long arm of a chromosome 21 at the first cleavage division of a normal zygote would probably result in an individual with Down's syndrome.

Some fathers of children with a presumptive 21/21–22 translocation (or isochromosome 21) have been found to be chromosomal mosaics, one of the cell lines being normal and the other

carrying the abnormal chromosome (Fraccaro *et al.,* cited by Hamerton *et al.,* 1961 *b*; Hamerton, 1962). This type of chromosomal anomaly may involve either an entire gonad or a part of a gonad.

The transmission of a presumptive 21/21–22 translocation (or isochromosome 21) is often through the father. The mean age of fathers of newborns with this type of chromosomal anomaly is reported to be higher than the mean age of parents of newborns with a presumptive 13–15/21 translocation, or of parents in the general population (Penrose, 1962).

In the present series two of the fathers of children with the presumptive 21/21–22 type of translocation (or isochromosome 21) were aged 40 and 50 years, respectively, at the time of birth of the affected child. The father of the third case was 24 years old at the time of birth of the affected child, and the age of the father of the fourth case was unknown.

Only one of the 92 isolated cases of Down's syndrome (Case 62) had a presumptive 13–15/21 translocation (Fig. 10). The parental karyotypes prepared from cultured blood and skin cells were apparently normal. The abnormal chromosome probably resulted from a reciprocal translocation between a chromosome 21 and a member of group 13–15. Individuals with Down's syndrome of this type are probably effectively trisomic for the long arm of chromosome 21. The presumptive translocation found in the patient under discussion probably occurred during gametogenesis in one of the parents. The situation is the same as in some other sporadic cases of Down's syndrome with a presumptive 13–15/21 translocation and normal parental karyotypes (Polani *et al.,* 1960; Ellis and Penrose, quoted by Penrose, 1962; Ellis, quoted by Penrose, 1962; Scherz, 1962; Dent *et al.,* 1963; Hyashi, 1963; Matsunaga *et al.,* 1963). In some of the sporadic cases (Hamerton *et al.,* 1961 *a*; Breg *et al.,* 1962 *a*; German *et al.,* 1962 *a*; Shaw, 1962; Hyashi, 1963) the affected child inherited a 13–15/21 translocation from the mother and in only one case from the father (Sergovich *et al.,* 1962).

Analyses of parental age data of cases of Down's syndrome with

a presumptive 13–15/21 translocation have shown that neither the father's nor the mother's age at the patient's birth differed significantly from parental ages at the time of birth in the general population (Penrose, 1962). The transmission of this type of translocation to an affected child is usually through the mother. The only known example of a paternal transmission of a probable 13–15/21 translocation to a child with Down's syndrome is that of Sergovich *et al.* (1962). The maternal age at birth of the case with a 13–15/21 translocation in the present series was 27 years.

The number of affected cases with a presumptive translocation or isochromosome involving chromosome 21 in this material was too small to allow any definite conclusions regarding the presence of a correlation between the occurrence of the translocation cases and maternal age at their births (Table 8).

The majority of presumptive translocations described in man have involved acrocentric chromosomes. It should, however, be remembered that translocations involving acrocentric chromosomes would be more easily observed and perhaps be less deleterious than translocations between other members of the complement. The increased risk for acrocentric chromosomes to undergo rearrangements is probably related to the presence of nucleolus-organizing regions in their short arms. The nucleolar fusion during interphase would tend to make satellited chromosomes lie adjacent to each other (Ferguson-Smith and Handmaker, 1961; Ohno *et al.*, 1961). This could explain the tendency for translocations between acrocentric chromosomes.

One of the nonfamilial cases (Case 52), a girl with typical Down's syndrome, was found to have 48 chromosomes including an extra small satellited metacentric chromosome (Fig. 12). Both arms of the latter chromosome resembled the short arms of the acrocentrics in length. Some patients with Down's syndrome and a presumptive 21/21–22 translocation (or isochromosome 21) have had a centric fragment in at least a portion of their cells (Penrose *et al.*, 1960; Migeon *et al.*, 1962). Gray *et al.* (1962) found a centric fragment in about a quarter of the cells of a girl with Down's syndrome having a similar karyotype. These authors interpreted

the karyotype as resulting from crossing over within a pericentric inversion. In one family normal carriers of a presumptive 13–15/21 translocation were found to have a centric fragment in some of their cells (German *et al.*, 1962 *a*). 48/46 chromosome mosaicism in a boy with Down's syndrome has been reported (Blank *et al.*, 1963). The cell line with 48 chromosomes had a karyotype similar to that of Case 52, with five chromosomes in group 21–22 and a satellited centric fragment. The cell line with 46 chromosomes had an extra chromosome in the 19–20 group and only three small acrocentrics. Cases of Down's syndrome with 47 chromosomes, including a small chromosome resembling the Ph[1] chromosome, have been reported. Two of these cases were boys with clearcut Down's syndrome (Hall, 1963 *b*). Another case with an additional small chromosome resembling the Ph[1] chromosome, a girl, was regarded as a case of "partial" Down's syndrome (Dent *et al.*, 1963). A child with features suggestive of Down's syndrome had a chromosomal fragment in a large proportion of cells (Ilbery *et al.*, 1961).

The origin of the chromosomal anomaly in Case 52 could be explained in several ways. The extra small metacentric chromosome could have arisen in the following ways:

(1) from the short arms in a reciprocal translocation between two acrocentric chromosomes,
(2) through misdivision of the centromere of one of the acrocentrics with the formation of an isochromosome for the short arm,
(3) through deletion of part of the long arm of an acrocentric chromosome.

These events might have occurred during gametogenesis in one of the parents or possibly after formation of the zygote.

Case 81 is a girl with typical Down's syndrome and 21-trisomy. Her only sib, a brother (Case 81 Br) (Fig. 31 *c*), has an extra small metacentric chromosome (Fig. 28). The chromosomal abnormality in Case 81 has probably occured as a result of nondisjunction in one of the parental gonads. The origin of the odd metacentric chromosome in her brother cannot be determined from its morpho-

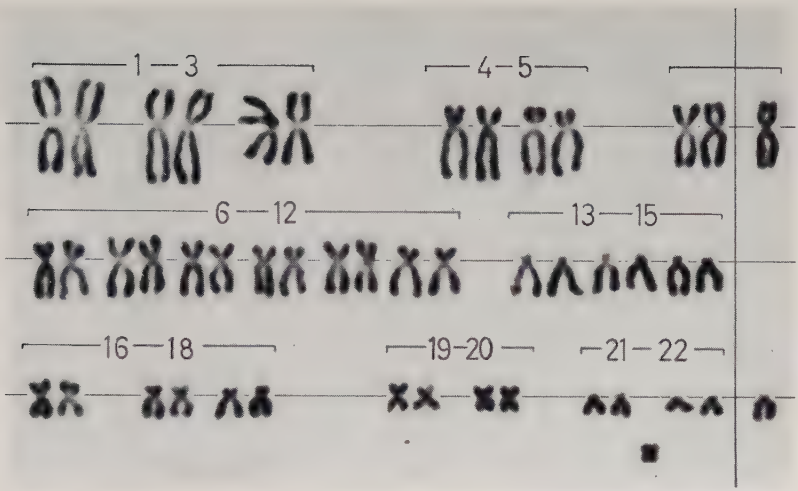


Fig. 28. Karyotype from Case 81 Br. There are 47 chromosomes, including an extra small metacentric chromosome (placed below group 21–22).

logical appearance or from clinical evidence. The clinical findings in the brother do not fit into any of the previously described syndromes related to autosomal abnormalities such as (13–15)-trisomy, (17–18)-trisomy or 21-trisomy. He had, however, a small mouth and muscular hypertonicity, which are frequently associated with the (17–18)-trisomy syndrome. A small metacentric chromosome similar to that found in Case 81 Br has been reported in a mentally retarded boy with some features in common with the present case (Frøland *et al.*, 1963). The odd metacentric chromosome in the present case could be the result of a translocation or a deletion. It could also represent an isochromosome for the short arm of a chromosome of pair no. 17 or 18. In the better quality metaphase plates the lengths of the arms of the abnormal chromosome appeared similar to the short arm of no. 18 rather than 17.

Since Case 81 Br is sex chromatin negative it is probable that the extra chromosome does not represent a deleted X. The chromosomal abnormalities in the two siblings under discussion could

be a matter of coincidence or they could more possibly be in some way related to each other. Some factor, probably genetic, in one of the parents could have predisposed to meiotic irregularities. Benirschke *et al.* (1962) have described a family in which the mother had given birth to a child with Klinefelter's syndrome (XXY), a normal male (XY), and a daughter with Down's syndrome with a 21/21–22 translocation. No translocated chromosome was found in any other member of this family. All three children had different fathers.

Parents of isolated cases of Down's syndrome usually have normal karyotypes (Makino *et al.,* 1962; Hamerton, 1962; Edwards *et al.,* 1963). In the present series, those parents of isolated cases of Down's syndrome who were investigated cytogenetically were found to have apparently normal karyotypes.

Familial Cases of Down's Syndrome

In the present series there were two siblings with Down's syndrome in each of two families. In addition, two other unrelated cases of Down's syndrome each had had one sibling with Down's syndrome. Another case of Down's syndrome also had a sibling with Down's syndrome who was not investigated cytogenetically. These seven cases were investigated because of the presence of familial Down's syndrome. Case 99 and her parents were studied because a paternal uncle of the affected child also had Down's syndrome.

One of the familial cases of Down's syndrome was a chromosomal mosaic (Case 29). All the other affected cases had 47 chromosomes with 21-trisomy. The parents of the affected sibs and the parents of Case 99 had apparently normal karyotypes. The fact that the parents of the affected sibs had normal karyotypes and that no translocation was detected in the affected sibs makes it possible that two random nondisjunctional events leading to 21-trisomy might have occurred in these families. It is also possible that some factor could have predisposed to nondisjunction or that one of the parents was a gonadal mosaic.

The mosaic pattern in Case 29 was found only in skin cultures (Fig. 8). The cells derived from blood all had 47 chromosomes with 21-trisomy.

The following interpretations of the mosaicism found in the cells of the skin of this patient are possible:

(1) A mosaic of cells with 46 (normal), 47 (trisomy 21) and 48 (trisomy 21 and trisomy 19 or 20) chromosomes. This type of mosaicism could have originated in several ways. Mitotic non-disjunction in a trisomic 21 embryo could result in one cell line with 48 (trisomy 21 and trisomy 19 or 20) chromosomes. The cell population with 46 (normal) chromosomes might have arisen from a cell with 47 (trisomy 21) chromosomes through anaphase lagging.

(2) The extra metacentric chromosome in the cells with 48 chromosomes could represent an isochromosome for the long arm of a small acrocentric chromosome or a 21/21–22 translocation. If this extra chromosome represents an isochromosome 21 or a 21/21 translocation the stem-line with 48 chromosomes would be pentasomic for the long arm of chromosome 21.

As the patient represents a very typical case of Down's syndrome it is most likely that the extra metacentric chromosome represents an isochromosome for the long arm of a chromosome 21 or a 21/21 translocation.

Cases in whom a Clinical Diagnosis of Down's Syndrome could not be made

Of the 57 individuals with suspected Down's syndrome in the present series, 18 did not fulfil the diagnostic criteria used by the author. Sixteen of these 18 individuals had an apparently normal karyotype and two had chromosomal aberrations (Cases 6 and 45).

Case 6, a girl whose karyotype was studied because of features suggestive of Down's syndrome, was found to have a total of 46 chromosomes with five small acrocentric chromosomes and only

one chromosome 16 (Fig. 11). The cells derived from skin cultures of the parents showed apparently normal karyotypes.

Several interpretations of the karyotype of this patient are theoretically possible. These are as follows:

(1) The patient could be trisomic for chromosome 21 or 22 and monosomic for 16. This is however unlikely as unquestionable monosomy for an autosome in man has not yet been found to be compatible with life.

(2) The additional chromosome in group 21–22 represents a deleted chromosome 16 with most of the long or short arm missing.

(3) The additional acrocentric chromosome has originated through a translocation between chromosome 16 and an acrocentric chromosome. It should then probably consist of the short arm of an acrocentric chromosome and the short or long arm of chromosome 16, assuming a point of exchange close to the centromere.

This patient probably lacks a considerable amount of chromosomal material. Deletion of the short arm of a chromosome 17 or 18 (Thieffry *et al.*, 1963) and deletion of the short arm of a chromosome 4 or 5 (Böök *et al.*, 1963; Lejeune *et al.*, 1963 *b*) have been described. Except for the deleted small acrocentric chromosome in individuals with chronic myeloid leukemia apparent deletions involving autosomes seem to be rare. DNA measurements of chromosomes might possibly detect small deletions and translocations not obvious with current methods (Rudkin *et al.*, 1962).

Case 45, a girl with some features characteristic of Down's syndrome, was found to have a chromosomal mosaicism of normal/trisomy 21 type. She is not classified as a case of Down's syndrome as her mental development has been normal. Chromosomal mosaics of normal/trisomy 21 type could arise from one or several possible mitotic events at the early post-zygotic stages.

Mitotic nondisjunction of chromosome 21 in a mitosis after the first cleavage division of a normal zygote would give origin to

cells with 45 and 47 chromosomes. The cell with 45 chromosomes would be monosomic for chromosome 21 and probably inviable. The result would then be a mosaic of type normal/trisomy 21.

In a zygote originally trisomic for chromosome 21, chromosome lagging at anaphase would give origin directly to two cell lines, one with 46 (normal) and one with 47 (trisomic 21) chromosomes.

The observation concerning a couple of monozygous male twins, one with 21-trisomy and the other with a normal karyotype, indicates that the abnormal segregation of chromosome 21 can occur as early as the second division of the zygote (de Wolff *et al.*, 1962).

Correlation between the Clinical and Cytogenetical Findings in the Group of Patients with Extra Genetic Material of Chromosome 21

It is realized that a comparison of the clinical findings between the patients with different abnormal karyotypes in the present series of Down's syndrome is baised because the patients were not selected on the basis of their karyotypes.

There was a great variability in the number and constellation of diagnostic signs among different cases. It is possible that this is due at least in part to the interaction between the three chromosomes 21 and the rest of the genotype.

As regards the diagnostic signs, it was not possible to differentiate the translocation type of Down's syndrome from the group with classic 21-trisomy. It appears also from the data reported in the literature that these two types of Down's syndrome probably cannot be distinguished on clinical grounds (Atkins *et al.*, 1962; Breg *et al.*, 1962 *a*; Shaw, 1962). That no striking clinical differences have been observed between patients with classic 21-trisomy and patients with the translocation type of Down's syndrome indicates that very little or no significant material has been lost in the formation of the translocation chromosome. Further indication of this is that the heterozygotes of these pre-

sumptive translocations, the "carriers", are apparently phenotypically normal.

Case 52 of the present material is a girl with 21-trisomy plus an extra small metacentric chromosome. No clinical features were found which could distinguish her from the usual 21-trisomics.

Clinical information concerning mosaicism involving chromosome 21 is still limited but there seems to be a good deal of phenotypical variation in individuals with this type of mosaicism. Thus, some of the mosaic cases have shown marked mental retardation and other features consistent with a diagnosis of Down's syndrome (Fitzgerald and Lycette, 1961; Richards and Stewart, 1962; Hyashi, 1963; Zellweger and Abbo, 1963). All of these patients had more than 50 per cent of abnormal cells in culture. Case 29 of the present series with mosaicism of type normal/trisomy 21/trisomy 21 plus isochromosome 21 was also a typical case of Down's syndrome. In this patient all cells derived from peripheral blood were trisomic for chromosome 21, and 78 per cent of cultured skin cells had extra genetic material of chromosome 21.

On the other hand mosaicism involving chromosome 21 has also been reported in individuals who are not mentally retarded and have either none or only a few physical features of Down's syndrome. (Clarke *et al.,* 1961, 1963; Fraccaro *et al.,* cited by Hamerton *et al.,* 1961 *b*; Hamerton, 1962; Edwards *et al.,* 1963. Cited by Verresen *et al.,* 1963; Weinstein and Warkany, 1963.) In most of these cases the majority of the cells examined had a normal chromosome constitution.

Case 45 of the present series, a girl with normal/trisomy 21 type of mosaicism, had some features of Down's syndrome but was lacking others such as mental retardation, brachycephaly, Brushfield spots and skeletal X-ray changes. The head circumference and dentition were normal as well as the palms and fingers. She had no four-finger lines and the dermal ridge patterns were not typical of Down's syndrome although they displayed some of the characteristics found in the syndrome. Thirty-five per cent of the cultured skin and blood cells of this patient had 47 chromo-

somes and were trisomic for chromosome 21. Sixty-one per cent of the cells had a normal karyotype.

The phenotypical expression of chromosome 21 probably varies with the "extra dose" of chromosome 21 present in the different tissues of these mosaic individuals. The different proportions of cells found in these individuals may vary from one tissue to another or from one individual to another because of the possibility of selective growth processes during development of the individual. It is obviously impossible to obtain a complete picture of the distribution of the mosaic patterns within and between different tissues and organs. Furthermore, the cultivation of cells *in vitro* may result in a change of proportions as compared with the proportions of the cell types found *in vivo*. Thus, in both patients with mosaicism in the series under discussion (Cases 29 and 45) there was a substantial variation of the proportions of the different cell types found in different cultures.

Chromosomal Aberrations Resembling those found in Down's Syndrome

Individuals not having specific features of Down's syndrome but with an extra small acrocentric chromosome have been reported. These individuals usually show varying clinical findings. In some of these cases the additional acrocentric chromosome has probably been the result of a translocation (Vieslie *et al.*, 1962; Jacobsen *et al.*, 1963). In Case 6 of the present series the extra small acrocentric chromosome probably was the result of a translocation or deletion involving chromosome 16.

In a patient described by Zellweger *et al.* (1962 *b*) a supernumerary small acrocentric chromosome probably represented a partially deleted member of group 13–15. This may also have been the situation in the two sisters of the present series not having Down's syndrome but with an extra small acrocentric chromosome (Cases I and II). An extra small acrocentric chromosome has in some cases probably been a Y chromosome (Sand-

berg *et al.*, 1961; Dent *et al.*, 1963, in reference to Hayward and Bower, 1960).

A specific syndrome associated with trisomy for chromosome 22 is at present not known. A few individuals with a small extra chromosome which could be a no. 22 have been reported but these cases show varying clinical findings (Dunn *et al.*, 1961; Turner and Jennings, 1961; Fitzgerald, 1962; Koulischer and Perier, 1962; Zellweger *et al.*, 1962 *a*; Beçak *et al.*, 1963; Hall, 1963 *a*; Haylock and Williams, 1963). Case III of the present series was trisomic for a chromosome of group 13–15 and, in addition, there was an extra chromosome in the small acrocentric group. The identity of the latter chromosome was not definitely established, but in the absence of signs of Down's syndrome it was thought to be a no. 22, a deleted member of group 13–15 or a Y chromosome.

Individuals not having specific features of Down's syndrome but with chromosomal aberrations morphologically resembling the 21/21–22 type of translocation (or isochromosome for the long arm of chromosome 21) found in cases of Down's syndrome have been reported.

An example of this is a boy with atrial septal defect and an abnormal karyotype reported by Böök *et al.* (1961 *b*): only three chromosomes in group 21–22 were present and there was an extra chromosome in group 19–20. Another example is Case IV of the present series, a male infant not having Down's syndrome with a presumptive 4–5/21–22 translocation morphologically resembling the 21/21–22 type of translocation found in cases of Down's syndrome.

Diagnostic Value of Chromosomal Analysis

In the 101 cases in whom a clinical diagnosis of Down's syndrome could be made in the present series, extra genetic material of chromosome 21 was found.

All published karyotyped cases of Down's syndrome, with one exception (Hall, 1962), have had extra genetic material of chromosome 21. However, in this case the diagnosis has been questioned by others (Hamerton and Polani, 1962).

It now seems clearly established that trisomy for chromosome 21 or effective trisomy for chromosome 21 such as has been described in cases of Down's syndrome with a presumptive translocation is a specific diagnostic finding.

Cases of mosaicism with a proportion of cells being trisomic for chromosome 21 have shown a range of stigmata varying from full-blown Down's syndrome to an apparently normal phenotype. This variability in phenotypic expression presumably is related to the proportion of cells in the body which are trisomic for chromosome 21.

It is sometimes difficult to make a clinical diagnosis of Down's syndrome during the first year of life. The greatest diagnostic difficulties arise in the neonatal period, especially in those children who are prematurely born. Although some signs may suggest Down's syndrome this condition may be wrongly diagnosed (Anell, 1945; Øster, 1953). The diseases considered in the differential diagnosis are myxedema, gargoylism and chondrodystrophy. The differential diagnosis from these diseases will, however, to-day usually not cause any difficulties (Øster, 1953; Cant, 1963). On the other hand, the diagnosis of Down's syndrome may be missed in other cases. Mental retardation, brachycephaly, flat nasal bridge, ear anomalies, short and incurved 5th fingers, muscular hypotonia and other features characteristic of Down's syndrome may be difficult or impossible to evaluate during the newborn period. In addition there is no one pathognomonic sign in Down's syndrome. Occasionally, otherwise normal individuals or mental defectives not having Down's syndrome show some of these features.

The diagnosis of Down's syndrome in a newborn child exerts deep and far-reaching effects upon the entire family, and sometimes it may take a long time before a definite clinical diagnosis can be made.

The observation by Caffey and Ross (1956, 1958) of the decrease in acetabular and iliac angles (Caffey's index) of the pelvis of an infant with Down's syndrome is probably one of the most objective clinical criteria for a diagnosis of this syndrome. In the present

material Caffey's index was measured in 46 infants with Down's syndrome below 12 months of age. Caffey's index was diagnostic in 31 (67 per cent) of these infants, i.e. it lay below −2 standard deviations. A Caffey's index typical of Down's syndrome has, however, also been found in infants with chondrodystrophia congenita punctata, rickets and paralytic abdominal lesions (Caffey and Ross, 1958; Schultze-Jena, 1959; Rudhe, personal communication).

Thirty-seven infants of the present series were 12 months old or younger when they were referred from pediatric clinics for chromosomal investigation because of suspected Down's syndrome. In 31 of the infants trisomy 21 or a presumptive translocation or isochromosome with effective trisomy of chromosome 21 was found by chromosomal investigation. Six infants were found to have apparently normal karyotypes and four of these have since then developed normally; one was later diagnosed as a case of unspecified mental deficiency, and another was later found to be slightly mentally retarded with a probable diagnosis of gargoylism.

The diagnostic value of chromosome analyses in suspected cases of Down's syndrome is evident from the above discussion.

SUMMARY

1. The main objectives of this investigation were:

(*a*) to collect original data for an analysis of chromosomal aberrations in a Swedish sample of patients with Down's syndrome (mongolism),

(*b*) to examine the significance of karyotype analyses in diagnosis, particularly when an unequivocal diagnosis based on clinical examination could not be made,

(*c*) to analyse the association between clinical signs and the different types of aberrant karyotypes occurring in patients with Down's syndrome,

(*d*) to examine other similar karyotype abnormalities in order to evaluate their significance in differential diagnosis.

2. The voluminous literature of Down's syndrome has been surveyed in a condensed form, including clinical as well as cytogenetical data.

3. In this investigation a sample of 119 individuals with Down's syndrome or suspected Down's syndrome has been examined. In addition 4 patients who displayed multiple congenital malformations not characteristic of Down's syndrome have been included because their karyotypes were of differential diagnostic interest.

Cytogenetical examinations have also been carried out on 53 relatives. Most of them were parents of patients with chromosomal aberrations.

4. The data from the clinical investigation were registered on a standard form, which included data concerning the family, birth, development and physical examination. All the data were personally collected by the author.

5. The criteria for a clinical diagnosis of Down's syndrome were mental retardation plus four or more of Øster's 10 "cardinal signs" for a diagnosis of Down's syndrome (Øster, 1953) (see p. 62).

The above diagnostic criteria were fulfilled by 101 of the 119 individuals previously diagnosed as having Down's syndrome or suspected Down's syndrome. Of these 101 individuals 94 were trisomic for chromosome 21, four had a presumptive 21/21–22 translocation (or alternatively a presumptive isochromosome for the long arm of chromosome 21), one had a presumptive 13–15/21 translocation, one had 48 chromosomes including an extra chromosome 21 and a small satellited metacentric chromosome, and one was a mosaic of type normal/trisomy 21/trisomy 21 plus isochromosome 21.

The remaining 18 individuals did not fulfil the above criteria for a diagnosis of Down's syndrome. An apparently normal karyotype was found in 16 of these individuals, one had a presumptive translocation or deletion involving chromosome 16 and one had normal/trisomy 21 mosaicism.

6. Ninety-two patients with Down's syndrome had no close relative with the disease. All but six of these 92 nonfamilial cases had 21-trisomy. Among the six cases four had a presumptive 21/21–22 translocation (or alternatively an isochromosome 21), one had a presumptive 13–15/21 translocation, and one had 48 chromosomes. Normal karyotypes were found in parents of nonfamilial cases of Down's syndrome when tissues were available for study. One of the nonfamilial cases with 21-trisomy had a brother with an extra small metacentric chromosome and the following features: microcephaly, mental retardation and epilepsy.

Nine patients were studied because they were examples of familial Down's syndrome. Of these patients eight had 47 chromosomes with 21-trisomy and one was a chromosomal mosaic involving chromosome 21 with three different cell types. The parents of eight of these familial cases were investigated and found to have normal karyotypes.

7. In 94 individuals with Down's syndrome and trisomic for chromosome 21 the distribution of chromosome counts has been studied in cultured cells derived from skin, bone marrow and peripheral blood. The proportion of cells with chromosome counts deviating from the modal number of 47 was 2.2 per cent.

8. The mean birth weights of females and males, respectively, with Down's syndrome were significantly lower than those of corresponding control groups. The mean duration of pregnancy was decreased in women who gave birth to children with Down's syndrome.

Furthermore, it was found that the growth rate with regard to stature decreased more markedly with increasing age in individuals with Down's syndrome compared to normals.

For 34 of 53 patients with Down's syndrome who had X-ray examinations of the hands the middle phalanx of the 5th finger was short and hypoplastic. X-ray examination of the pelvis with calculation of the iliac index (Caffey's index) was made in 46 infants with Down's syndrome below 12 months of age. Caffey's index was diagnostic for 31 of the 46 infants.

The patients with Down's syndrome showed a great variability with respect to the number and combination of diagnostic signs. It was not possible to differentiate the translocation type of Down's syndrome from the group with classic 21-trisomy by the criteria used in this investigation.

9. In the present sample 37 infants were 12 months old or younger when they were referred for chromosomal examination because Down's syndrome was suspected. Of these, 31 infants had extra genetic material of chromosome 21 in either the form of a trisomy, a presumptive translocation or a presumptive isochromosome; six infants were found to have apparently normal karyotypes. Of these latter six infants, four have since developed normally, one has been diagnosed as having unspecified mental deficiency, and one has been classified as mentally retarded with probable gargoylism.

APPENDIX

Case Reports of Cases 1–101 and Cases S1–S16

Case 1 (21-trisomy), born in 1948, is a boy with typical Down's syndrome. He cannot talk or understand when spoken to and has urinary and fecal incontinence.

Case 2 (21-trisomy), born in 1940, is a male with typical Down's syndrome. He cannot talk or understand when spoken to and has urinary and fecal incontinence. A male cousin of the paternal grandfather is mentally retarded but he does not have Down's syndrome.

Case 3 (21-trisomy), born in 1929, is a female with typical Down's syndrome. She cannot talk or understand when spoken to and has urinary and fecal incontinence.

Case 4 (21-trisomy), a boy, was born in 1959. Immediately after birth he was transferred to a pediatric clinic because of suspected Down's syndrome. Slightly oblique palpebral fissures, bilateral epicanthus, a flat nasal bridge, slightly malformed ears, congenital heart defect, muscular hypotonia and slight jaundice were noted. The total serum bilirubin reached its maximum (20.4 mg%) on the 8th day after birth. No blood group incompatibility was found.

He has been readmitted several times to the clinic because of congenital heart disease with cardiac decompensation. Physical examination by the author when the patient was 2 8/12 years old showed a clearcut case of Down's syndrome. He began to sit at 18 months and to walk at 3 1/2 years, but he was unable to talk at 4 years of age.

Case 5 (21-trisomy), a boy, was born in 1959. He was transferred to a pediatric clinic immediately after birth because of pronounced cyanosis and features characteristic of Down's syndrome. Oblique palpebral fissures, epicanthic eye-folds, malformed ears, a four-finger line, hyperflexibility of the joints and muscular hypotonia were noted. The child died 6 hours after birth. The autopsy diagnoses were: Down's syndrome, aortic stenosis, persistent ductus arteriousus, and atresia of esophagus.

Case 6 (Monosomic 16, trisomic 21 or 22? Deletion or translocation involving 16?), a girl, was born in 1956. Her mother, born in 1929, is healthy and the index case is her only child. There have not been any abortions. The father, born in 1925, is healthy and has three normal children by a previous marriage. The mother was healthy during the pregnancy and the patient was born at full term by an uncomplicated breech presentation.

The patient was admitted to a pediatric clinic at the age of 9 months because of constipation and retarded development. She had slightly reduced muscular tonus and hyperflexible joints, a broad nasal bridge, left-sided strabismus, smaller than normal palpebral fissures, bilateral epicanthus, a preauricular papilloma on the left side and misshapen prominent ears.

Roentgenograms of the hip-joints showed both caput femori dislocated above the articular cavity. X-ray films of the skeleton revealed an approximate three month retardation in bone age.

Ophthalmoscopic examination revealed retinal degeneration with scattered white spots in both optic fundi. The optic discs were normal. An electroretinogram showed no pathological changes.

Because of a continued tendency to dislocation of the hips bilateral sub-trochanteric osteotomies were performed in 1959.

At the age of two years she was admitted to a pediatric clinic because of retarded development and some features suggestive of Down's syndrome. She has been readmitted several times. The last time was at 3 10/12 years of age. Her height has always been below normal. However, her weight in relation to her height has been normal.

X-ray films of the head showed a somewhat small calvarium. No intracranial calcifications were visible. There were no deformities of the facial region or of the base of the skull. Roentgenograms of the skeleton showed a normal number of ossification centers with respect to the height but fewer than normal with respect to the age. The bones were slender. No deformities of the middle phalanges of the little fingers were visible. An intravenous urogram was normal as were roentgenograms of the heart and lungs.

An electrocardiogram and an electroencephalogram were likewise normal.

An estimate of her development made at the age of 3 years showed that fine motor movements and adaptive development were equivalent to that of a child of 2 years. The patient walked at 3 5/12 years of age. She could speak single words at the age of 3 years.

Evaluation of her intellectual development at 3 7/12 years of age showed a general level corresponding to a 2 6/12 year old child. A Leiter test at 6 years of age gave an IQ of 60. The patient has always been easy

to handle. She is cheerful and likes to sing and listen to music. Her general health has always been good. Apart from a chronic blepharitis, no infections have been reported.

Physical examination at 3 10/12 years of age showed a somewhat small girl with a rather odd appearance (Fig. 29 *f*). The head circumference was 45 cm and the cephalic index 84. The height was 88 cm and the weight 13 kg. There were typical epicanthic eye-folds bilaterally. The palpebral fissures were narrow, and there was slight blepharitis bilaterally. The nose was flat and relatively small with a broad bridge. The ears were misshapen and prominent. The tongue was normal in size without papillary hypertrophy or deep furrows, and it was not protruding. The position and the shape of the teeth were normal, but there were extensive caries and paradentosis. The hands were relatively short and broad with short little fingers. The feet were small and short and in a typical planovalgus position. The joints were hyperflexible and there was generally decreased muscular tonus. No signs of congenital heart disease were noted. The configuration of the thorax, the abdomen and the external genitalia were all normal. Further routine physical and neurological examination showed no apparent abnormalities. No four-finger line was present.

The dermal ridge patterns of the hands and feet do not suggest a diagnosis of Down's syndrome, indeed they practically exclude it (Professor L. S. Penrose).

Although the patient has some signs and symptoms suggestive of Down's syndrome, others such as her general appearance and the dermal ridge patterns of hands and feet contradict this diagnosis.

Case 7 (21-trisomy), a boy, was born in 1950. The mother had a rubella-like rash for 3 days during the first month of pregnancy. Down's syndrome and congenital cataract were diagnosed at birth. The cataract was operated upon when he was 5 months old. When he was admitted to a pediatric clinic at 9 years of age for a developmental test, several features characteristic of Down's syndrome were noted, and his mental development was found to be below that of a 3-year-old child. X-ray films showed a normal pelvis.

Case 8 (21-trisomy), a boy, was born in 1959. Down's syndrome was diagnosed at 3 months of age at a pediatric clinic. A Gesell test at 3 3/12 years of age showed a development corresponding to that of a 1 6/12 year-old child. The karyotypes of the parents are normal.

Case 9 (21-trisomy), a girl, was born in 1959. Features characteristic of Down's syndrome were noted at birth. This diagnosis was confirmed

at a pediatric clinic where the patient was admitted at 1 month of age because of failure to thrive. She died of an infection at the age of 7 weeks. The karyotypes of the parents are normal.

Case 10 (21-trisomy), a boy, was born in 1957. The mother had had 2 spontaneous abortions during a previous marriage.

He was transferred to a pediatric clinic immediately after birth because of cyanosis and features suggestive of Down's syndrome.

Re-examination in the clinic at 2 6/12 years of age showed many features typical of Down's syndrome. A Gesell test showed a motor age of 18 months. Speech and adaptive development were equivalent to a child of 15 months.

Physical examination by the author when Case 10 was 5 2/12 years old showed a mentally retarded boy with clearcut Down's syndrome. There was also syndactyly of the 2nd and 3rd toes bilaterally.

Case 11 (21-trisomy), a boy, was born in 1960. He was the third of three siblings. The mother had a spontaneous abortion in 1946. Her second child has ulcerative colitis. The index case was transferred to a pediatric clinic immediately after birth because of cyanosis and features suggestive of Down's syndrome. There was neonatal icterus with a maximum total serum bilirubin concentration of 15.2 mg/100 ml on the 5th day after birth. Angiocardiography at 16 months of age showed an atrial septal defect of the secundum type. Pronounced anemia and thrombocytopenia were found at 1 10/12 years of age. Acute myeloblastic leukemia was diagnosed at 2 6/12 years of age because of a bone marrow aspirate, which showed 35 per cent myeloblasts, and high white-cell counts in the peripheral blood with more than 70 per cent myeloblasts. He was then described as a definite case of Down's syndrome. A Bühler–Hetzer developmental test at 1 10/12 years of age gave a quotient of 53. He died at 2 6/12 years of age. The karyotypes of the parents are normal.

Case 12 (21-trisomy), a boy (Fig. 29 *a*), was born in 1959. He was admitted to a pediatric clinic when he was 24 days old because of persistent jaundice and suspected Down's syndrome. Microscopical examination of a liver biopsy specimen showed giant cell hepatitis.

Because of fever and dyspnea at 15 months of age the child was readmitted to the clinic where he expired the day after admission. At that time characteristic features of Down's syndrome including retarded development were present. In addition, a left-sided inguinal hernia was noted. The autopsy diagnoses were Down's syndrome, cardiac interventricular septal defect, hypoplasia of the pulmonary artery with stenosis of the left pulmonary ostium, abscess of right lower lobe of lung and hepatic abscess.

Case 13 (21-trisomy), a boy (Fig. 30 *e*), was born in 1960. After birth he was immediately transferred to a pediatric clinic because of features suggestive of Down's syndrome.

Physical examination by the author when the patient was 1 1/12 years old showed a typical case of Down's syndrome. His development has been retarded. He began to sit at 1 6/12 years, but he could not talk or walk at 3 4/12 years of age.

Case 14 (21-trisomy), a girl, was born in 1959. The mother had had two previous spontaneous abortions. The diagnosis of Down's syndrome was made at a pediatric clinic at 10 months of age. Physical examination by the author when the patient was 3 5/12 years old showed a typical case of Down's syndrome. There was syndactyly of the 4th and 5th toes bilaterally. Her development has been retarded. She began to walk at 3 1/12 years and could only say a few simple words at 3 5/12 years of age.

Case 15 (21-trisomy), a girl, was born in 1959. Features of Down's syndrome were noted at birth and the diagnosis was confirmed in a pediatric clinic where she died at the age of 7 months of an infection.

Case 16 (21-trisomy), a boy, was born in 1959. His mother had had one previous stillbirth. Two brothers have bilateral hydronephrosis, and a maternal uncle died at 26 years of age from "contracted" kidneys. Immediately after birth the index case was transmitted to a pediatric clinic where features of Down's syndrome were noted. There was neonatal icterus with a maximum total serum bilirubin concentration of 18 mg/100 ml on the 4th day after birth. He was readmitted at 10 months of age because of tetany which responded to vitamin D therapy. Physical examination by the author when the patient was 3 2/12 years old showed a typical case of Down's syndrome. He began to sit at 15 months, to walk at 2 years of age. He could not speak at 4 years of age.

Case 17 (21-trisomy), a girl, was born in 1960. Immediately after birth she was transferred to a pediatric clinic because of suspected Down's syndrome. Physical examination by the author when the patient was 2 6/12 years old showed a definite case of Down's syndrome. She began to sit a 2 years and could not walk or talk at 3 7/12 years of age.

Case 18 (21-trisomy), a boy, was born in 1960. Down's syndrome was diagnosed at birth. His development has been retarded. He began to sit at 2 7/12 years and could not walk or speak at 3 1/12 years of age.

Case 19 (21-trisomy), a boy, was born in 1960. At 9 months of age he was admitted to a pediatric clinic because of suspected Down's syndrome.

He was readmitted at 2 3/12 years of age because of an upper respiratory infection. He was then described as a definite case of Down's syndrome. X-ray films showed changes in the pelvic bones characteristic of Down's syndrome. His development has been retarded. He learned to walk at 3 2/12 years and could not speak at 3 5/12 years of age.

Case 20 (21-trisomy), a girl (Fig. 29 *c*), was born in 1960 as the first of probable dizygotic twins. The other twin is a normal girl. The diagnosis of Down's syndrome was made the day after birth in a pediatric clinic. Development has been retarded. She could not walk or speak at 3 6/12 years and she began to sit at 1 11/12 years of age.

Case 21 (21-trisomy), a boy, was born in 1960. His mother had previously been operated upon because of toxic goiter. The father has very short fifth fingers with marked clinodactyly and a four-finger line bilaterally. Three sisters of the index case as well as a paternal aunt and her daughter have marked bilateral clinodactyly.

Immediately after birth the index case was admitted to a pediatric clinic because of suspected Down's syndrome. At three months of age the diagnosis of a probable atrial septal defect was made. Physical examination by the author when the patient was 2 6/12 years old, showed definite features of Down's syndrome. He had bilateral retroposition of the 4th toe. His development has been retarded. He began to walk at 2 years and could not speak in sentences at 3 6/12 years of age.

Case 22 (21-trisomy), a boy, was born in 1960. He was transferred from the maternity ward to a pediatric clinic because of features suggestive of Down's syndrome.

Physical examination by the author when the patient was 2 3/12 years old showed definite features of Down's syndrome. Syndactyly of the 2nd and 3rd toes was noted bilaterally, and there was retroposition of the 4th toes. His development has been retarded. He began to sit at 1 year, and could not walk or talk at 3 5/12 years of age.

Case 23 (21-trisomy), a girl, was born in 1960. She was admitted to a pediatric clinic immediately after birth, because of a congenital heart defect. At that time a diagnosis of typical Down's syndrome was made. She died at 2 months of age. The autopsy diagnoses were Down's syndrome, congenital heart disease with atrial septal defect and an interventricular septal defect.

Case 24 (21-trisomy), a girl, was born in 1953. The mother had had one previous spontaneous abortion. Down's syndrome was suspected at birth

and the diagnosis was confirmed at a pediatric clinic at 7 years of age. She began to sit at 1 year, to walk at 1 8/12 years, to say a few simple words at 3 years and to speak in sentences at 9 years of age.

Case 25 (21-trisomy), a boy (Fig. 29 *b*), was born in 1960. He was transferred to a pediatric clinic immediately after birth because of suspected Down's syndrome. There was neonatal icterus with a maximum total serum bilirubin concentration of 19.6 mg/100 ml on the 4th day after birth. Physical examination by the author when the patient was 1 11/12 years old showed definite features of Down's syndrome. His development has been retarded. He began to sit at 19 months and could not walk or talk at 3 years of age.

Case 26 (21-trisomy), a girl, was born in 1960. During the first part of the pregnancy there was a threatened abortion. The mother had had 2 previous spontaneous abortions. The index case was transferred from the obstetrical ward to a pediatric clinic 7 days after birth because of Down's syndrome with congenital heart defect. She has since then been admitted several times to a pediatric clinic because of repeated upper respiratory infections. Examinations of the heart showed a probable persistent ostium A–V communis. Her development has been retarded. She could not sit, stand, walk or say any single words at 2 years of age.

Case 27 (21-trisomy), a girl (Fig. 29 *d*), was born in 1960. The mother's first pregnancy resulted in premature twins who died shortly after birth. No congenital malformations were noted. The index case was admitted to a pediatric clinic immediately after birth because of features suggestive of Down's syndrome. She was operated upon shortly after birth because of duodenal atresia. Physical examination by the author when the patient was 1 month old showed definite features of Down's syndrome. Her development has been retarded. She learned to sit at 1 4/12 years, to walk at 2 4/12 years, but could not say any single words at 2 9/12 years of age.

Case 28 (21-trisomy), is a male, born in 1946 with typical Down's syndrome. His mental development at 12 years of age corresponded to that of a child of 3 years. The mother has been pregnant three times. The first pregnancy resulted in a prematurely born boy who died 6 hours after delivery. Autopsy showed a patent foramen ovale and a pulmonary hyaline membrane. No features of Down's syndrome were observed. The index case was the second pregnancy. He was born when the mother was 31 years old.

The third pregnancy resulted in a girl with Down's syndrome. She was born when the mother was 37 years old and the diagnosis was

confirmed at a pediatric clinic. It was not possible to do a chromosome analysis.

No other cases of Down's syndrome, congenital malformation or mental retardation are known among the near relatives. The karyotypes of the parents are normal.

Case 29 (normal/trisomy 21/trisomy 21 plus isochromosome 21 mosaic), is a boy with Down's syndrome born in 1949. He is the third of six siblings. A brother with Down's syndrome, born in 1947, died at six months of age. A maternal aunt died at the age of 6 years of acute lymphatic leukemia. There are no other cases of Down's syndrome, multiple malformations or mental retardation known among the near relatives.

The index case has several signs normally associated with Down's syndrome—e.g. brachycephaly, oblique palpebral fissures, Brushfield spots, epicanthic eye-fold, a flat nasal bridge, a large protruding and furrowed tongue, a high-arched and narrow palate, short broad hands with short fifth fingers, a typical four-finger line on the right hand, and a pronounced gap between the first and second toes. His joints are somewhat hyperflexible, and muscular tonus is slightly decreased. The dermal ridge configurations on the palms and soles are strongly indicative of Down's syndrome. There is only one exceptional feature, namely a radial loop on the left index finger, a finding which is uncommon in Down's syndrome (Professor L. S. Penrose).

There were no signs of congenital heart disorder. No anomalies of sex development were found. Both testes were descended and of normal size. He lives in an institution for mental defectives, and his development at 11 years of age corresponded to that of a 4 year old child.

Case 30 (21-trisomy) is a female, born in 1936, with typical Down's syndrome. She is markedly mentally retarded and cannot talk or understand when spoken to.

Her mother has been pregnant 3 times. The first pregnancy resulted in a normal boy, the second in a girl with typical Down's syndrome (who died in a pediatric clinic at 1 month of age), and the third is the index case. The first girl with Down's syndrome was born when the mother was 36 and the father 37 years old; the index case was born one year later. Both parents are healthy and no further cases of Down's syndrome, malformations or mental retardation are known among their relatives. The karyotypes of the parents are normal.

Case 31 (21-trisomy) is a mentally retarded boy with typical features of Down's syndrome born in 1938. In addition he has a marked gibbous

secondary to a tuberculous spondylitis. There is retroposition of the 4th toes. His mother has been pregnant 3 times. The first pregnancy resulted in a boy who sustained a severe brain lesion at birth and died at 2 years of age. The second pregnancy resulted in the index case, who was born when the mother was 39 and the father 31 years old. The third pregnancy resulted in a girl with Down's syndrome (Case 32). Both parents are healthy and there are no further cases of Down's syndrome, malformations or mental retardation in the pedigree. The karyotypes of the parents are normal.

Case 32 (21-trisomy), the sister of Case 31, is a typical case of Down's syndrome. She was born when the mother was 41 years old. A Terman–Merrill test at 17 years of age gave an IQ of 39.

Case 33 (21-trisomy), a mentally retarded girl, born in 1954, was admitted to a child psychiatric clinic because of suspected Down's syndrome at 6 years of age. Clinical examination showed several features characteristic of Down's syndrome and a Terman–Merrill test gave an IQ of 45.

Case 34 (21/21–22 translocation or isochromosome long arm 21), a girl (Fig. 30 *f*), was born in 1960. At that time the mother was 30 and the father 40 years old. The patient's parents were married in 1955. No cases of Down's syndrome, malformations, mental retardation or other relevant conditions had been recorded among their relatives.

Extensive pulmonary sarcoidosis had been discovered in the father in 1950 and, in the succeeding ten years, he had repeated chest X-ray examinations. In 1957, following a complaint of sterility, two seminal specimens from the father were examined. The volume of seminal fluid, the sperm count per ml, and the motility of the spermatozoa were normal. Differential counts, based on examination of 400 spermatozoa by phase contrast microscopy, showed the presence of about 50% of morphologically abnormal forms.

The mother had no history of serious illness or abortions. In 1958 she gave birth to a boy whose subsequent health and development have been normal. Her second pregnancy which resulted in the index case was uneventful.

The patient was first referred for medical investigation at the age of five months after repeated upper respiratory tract infections and an episode of acute gastro-enteritis. Her clinical picture at this time was somewhat suggestive of Down's syndrome, and a skin biopsy was taken for chromosome analysis.

Five months later she was admitted to a pediatric clinic because of

dysphagia and suspected developmental retardation. On physical examination slight muscular hypotonia and joint hyperflexibility were noted. Peripheral non-physiological pigmentation of both fundi was observed on ophthalmoscopic examination. There were no Brushfield spots. She had slightly oblique palpebral fissures, slight bilateral epicanthus and a flat nasal bridge. The upper helix of the right ear was overlapping so that the margin formed a right angle with the descending part of the helix. The configuration of the ears was otherwise normal. Her tongue was normal with no protrusion, fissures or papillary hypertrophy. She had only two lower central incisor teeth, both showing irregular alignment. The palate was not high-arched or narrow.

Her hands were relatively short and a four-finger line was present on the left hand. The little fingers were normal in size and shape. The feet were somewhat short but there was no unusual gap between the first and second toes.

Muscular tone was slightly decreased and some joint hyperflexibility was noted. The examination of the thorax, abdomen and external genitalia was normal. No signs of congenital heart disease were elicited and there was no persistence of primitive reflexes. Routine physical and neurological examination failed to reveal any further abnormalities. X-ray examination showed a normal pelvis.

A Gesell test at 10 months of age showed motor development equivalent to a child of 6 months, adaptive and social development equivalent to a child of 8 months.

Her development since the age of one year has been clearly retarded. She began to sit at 15 months of age and to walk at 3 years of age. Although she was able to speak single words at 1 3/12 years of age, at the age of 3 6/12 years she was still unable to say short sentences and had urinary and fecal incontinence.

Case 35 (21-trisomy) is a girl born in 1961. Polyhydramnios was noted during the pregnancy. Delivery was normal. She was admitted to a pediatric clinic at the age of 4 weeks because of persistent jaundice and suspected Down's syndrome.

The jaundice was pronounced and of the obstructive type. A liver biopsy specimen showed intrahepatic obstructive jaundice. The white-cell count increased from 15,000/cmm at the time of admission to 148,000/cmm the day before death. The differential white-cell count showed a marked shift to the left with a high percentage of nucleated red cells. A bone marrow aspirate showed a leukemoid reaction. There were features characteristic of Down's syndrome such as flat occiput, a high cephalic index (92), oblique palpebral fissures, slight left-sided

epicanthus, slight blepharitis, prominent ears with a slightly folded upper helix, congenital heart disease, an atypical four-finger line on the left palm and increased distance between the first and second toes bilaterally. Muscular hypotonia and hyperflexibility of the joints were noted. Her general condition remained poor and she expired at 2 months of age.

Case 36 (21-trisomy), a boy, was born in 1960. The mother, who had been pregnant 3 times, had pulmonary tuberculosis in 1959. The first pregnancy resulted in a normal boy, the second terminated in a spontaneous abortion. The index case was the third pregnancy. Slightly oblique palpebral fissures, slight bilateral epicanthus, atypical four-finger line on the right palm, umbilical hernia and slight muscular hypotonia were noted at birth. A chromosomal investigation was made because of suspected Down's syndrome.

Physical examination at 22 months of age showed typical features of Down's syndrome with short stature, flat occiput, oblique palpebral fissures, Brushfield spots, blepharitis, high-arched and narrow palate, short fifth fingers, atypical four-finger line on the right palm, marked hypotonia and hyperflexibility of the joints. The child is highly susceptible to infections. His development has been retarded. He could not sit until 10 months of age and could not stand, walk or speak single words at 22 months of age.

Case 37 (21-trisomy), a boy, was born in 1961. There was only one umbilical artery. He was the third of 3 siblings and was born when the mother was 39 and the father 40 years old.

Brachycephaly, short and broad hands, short and incurved 5th fingers, a four-finger line on both palms, umbilical hernia, marked muscular hypotonia and hyperflexibility of the joints were noted at birth. He was also found to have epicanthic eye-folds, a flat nasal bridge, and a high-arched, narrow palate.

A chromosomal analysis was made because of features characteristic of Down's syndrome. He died at 3 months of age from an acute enterocolitis. The autopsy diagnoses were Down's syndrome and enterocolitis.

Case 38 (21-trisomy), a girl, was born in 1961. She was admitted to a pediatric clinic at 4 months of age because of suspected Down's syndrome. Bilateral epicanthus, oblique palpebral fissures, a large tongue, brachycephaly, an atypical four-finger line on each palm, slight muscular hypotonia and umbilical hernia were noted. The development has been retarded. She began to sit at 10 months of age, to walk at 2 6/12 years of age. She could only say a few simple words at 2 9/12 years of age.

Case 39 (21-trisomy) was a mentally retarded boy with typical features of Down's syndrome, born in 1947 when the mother was 22 and the father 29 years old. The diagnosis was made at a pediatric clinic in 1948 and a Terman–Merrill test in 1959 gave an IQ of less than 30.

The mother has been pregnant three times. The first pregnancy resulted in the index case, the second in a girl with Down's syndrome (Case 40) and the third was terminated by a legal abortion.

Both parents are healthy and normal and there are no further known cases of Down's syndrome, malformations or mental retardation in the pedigree. The parents' karyotypes are normal.

Case 40, the sister of Case 39, is a typical case of Down's syndrome born in 1949. This diagnosis was made at birth. A Terman–Merrill test in 1959 gave an IQ of 30. The patient is followed regularly in an outpatient clinic because of a congenital heart defect.

Case 41 (21-trisomy), a male dwarf with Down's syndrome, was born in 1947. No neonatal complications were encountered. The parents are normal and healthy, and there are no known cases of Down's syndrome or dwarfism among their relatives.

Down's syndrome was suspected at birth and this diagnosis was confirmed at a pediatric clinic when the patient was 2 months old. Since birth there has been marked retardation in growth and in physical and mental development.

Examination at 14 years of age showed a normally proportioned dwarf with Down's syndrome. His height was 106 cm (normal, 165 cm) and his weight 13.3 kg. He showed marked retardation in growth and development with idiocy; inability to talk, sit, stand or walk; underdeveloped musculature with hypotonia; marked hyperflexibility of the joints; ptosis of both eyes and lens opacities.

Case 42 (21/21–22 translocation or isochromosome long arm 21), a girl (Fig. 30 *a*), with typical Down's syndrome, was born in 1950 when the mother was 18 years old. The father was unknown. No cases of Down's syndrome, mental retardation or congenital malformations were known among the relatives of the mother. The mother, since then married with another man, has been pregnant three times and the index case was the result of her first pregnancy. The second pregnancy resulted in a stillborn girl with erythroblastosis fetalis and bilateral cheilochisis. The third pregnancy resulted in a boy with hemolytic disease due to Rh incompatibility. Exchange transfusion was done immediately after birth and his subsequent development has been normal.

The mother had rubella during the 6th month of gestation of the

index case. The development of the index case was retarded and she has been at an institution for mentally retarded children since 6 years of age. A Terman–Merrill test at 7 years of age gave an IQ of 36.

Physical examination at 11 years of age showed typical features of Down's syndrome. X-ray examinations at the same age showed that the phalanges of the fifth fingers were slightly smaller than normal. The pelvis was normal, and there was a suggestion of a slight valgus deformity of both femora. The mother has a normal female karyotype.

Case 43 (21-trisomy), a boy, was born in 1961. Down's syndrome was suspected at birth and he was admitted to a pediatric clinic where the diagnosis was confirmed.

His development has been markedly retarded. At 2 5/12 years of age he was unable to say any single words, sit, stand or walk.

Case 44 (21-trisomy), a boy (Fig. 30 *d*), was born in 1958. The mother, maternal grandmother and two maternal aunts have very short fifth fingers, which reach the first interphalangal joint of the 4th finger. The index case was transferred to a pediatric clinic immediately after birth. At that time features suggestive of Down's syndrome were noted. He was readmitted to the clinic at 2 9/12 years of age because of retarded development and suspected Down's syndrome. X-ray films showed hypoplasia of the second and third phalanges of the fifth finger and radiological examination of the pelvis showed changes characteristic of Down's syndrome.

His development at 3 3/12 years of age corresponded to 1 9/12 years according to the Vineland social maturity scale. Physical examination by the author when the patient was 4 years old showed a mentally retarded boy with clearcut Down's syndrome.

Case 45 (Normal/21-trisomy mosaic), a girl (Fig. 31 *a, b*) born in 1959, is the only child of healthy parents. She was born at term when the mother was 38 and the father 29 years old. At the age of 17 months she was admitted to a pediatric clinic because of susceptibility to infections and suspected Down's syndrome. Roentgen examination showed no skeletal malformations. There was no sign of congenital heart defect and an ECG was normal.

She was readmitted to the clinic at 27 months of age. X-ray films showed that the number and shape of the ossification centers were within normal range.

Laboratory findings. At the age of 27 months the protein-bound iodine was 6.1 gamma per cent. Triidothyronine uptake by erythrocytes was 23.8 per cent (normal, 12–20 per cent). The urinary excretion of 5-hydroxy-indol-acetic acid was 2.7 mg per day, a value within the range

found in normal individuals (Jérôme *et al.*, 1960). There were no reducing substances or phenylpyruvic acid in the urine.

The electrophoretic pattern of the serum proteins was normal.

Analysis of dermal ridge patterns (Professor L. S. Penrose). The palmar patterns do not show any unusual features. Finger tip patterns: the absence of arches and the presence of only one small whorl as well as the total ridge count being slightly below the normal are consistent with the diagnosis of Down's syndrome. In the soles open field patterns are present on both hallucal areas. This pattern is found in 75 per cent of individuals with Down's syndrome and only in 10 per cent of normals.

Physical examination at 28 months of age showed some features suggestive of Down's syndrome such as oblique palpebral fissures, slight left-sided epicanthus, a flat nasal bridge, a protruding tongue, a high-arched and narrow palate, and increased distance between the first and second toes bilaterally. Her joints were hyperflexible, and muscular hypotonia was noted. The height was 84 cm (normal, 90 cm) and the head circumference 48 cm (normal). There were no brachycephaly, macroglossia or Brushfield spots. The dentition was normal. The hands were normal, and there were no four-finger lines on the palms.

At 6 months of age the first tooth erupted and she began to sit. She crawled at 8 months, stood at 14 months and walked at 23 months. She was able to speak sentences at 34 months of age. A Gesell test at 27 months of age showed development of gross motor behavior corresponding to 24, fine motor behavior to 28, adaptive behavior to 24–26 and language to 21 months of age.

The karyotypes of the parents are normal.

Case 46 (21-trisomy), a girl, was born in 1961. Her development was retarded and she was admitted to a child psychiatric clinic because of suspected Down's syndrome at the age of 2 6/12 years. Several features typical of Down's syndrome were noted. X-ray films showed changes in the pelvic bones characteristic of Down's syndrome.

Physical examination by the author when the patient was 3 4/12 years old showed most of the features characteristic of Down's syndrome. She had learned to walk at 2 6/12 years of age, but at 3 4/12 years she was unable to speak in sentences and had urinary and fecal incontinence.

Case 47 (21-trisomy), is a female with Down's syndrome born in 1919. She lives in an institution for mental defectives. Physical examination in 1962 showed an underdeveloped right breast with a small nipple, similar to a male breast. The left breast was normally developed. The pubic hair was scanty and the axillary hair was lacking. Pelvic examination revealed no abnormalities of the external or internal genitalia.

Case 48 (21-trisomy) is a girl with Down's syndrome born in 1961. Physical examination by the author when the girl was 1 month old showed a typical case of Down's syndrome. The development has been retarded. She began to sit at 17 months and to crawl at 18 months of age. She was still unable to stand, walk or say single words at 2 years of age.

Case 49 (21-trisomy), a boy, was born in 1961. 5 days after birth he was admitted to a pediatric clinic because of feeding difficulties. 10 months later he was admitted to the clinic again because of an upper respiratory infection. His clinical picture at this time was suggestive of Down's syndrome. Physical examination by the author when the boy was 21 months old showed several features of Down's syndrome such as Brushfield spots, epicanthic eye-folds, blepharitis, a flat nasal bridge, a high-arched and narrow palate, a permanently open mouth with macroglossia, short broad hands with short fifth fingers, and an atypical four-finger line on the left hand. The skin was dry. The general appearance at that time was that of a child with Down's syndrome. The development had been retarded; he began to sit at 1 year of age, to walk at 2 years and he could only say a few single words at 2 1/12 years of age.

Case 50 (21-trisomy), a girl, was born in 1961. A diagnosis of Down's syndrome was made shortly after birth.

An older brother died at the age of 1 month from congenital heart disease. The index case was operated upon at the age of 6 months because of a diaphragmatic hernia. There was syndactyly of the 3rd and 4th toes bilaterally. She had also retroposition of the 3rd toes. Her development has been retarded. She learned to sit at 2 years but could not stand, walk or say any single words at 2 3/12 years of age.

Case 51 (21-trisomy), a boy, was born in 1961. Slight neonatal icterus was noted. He was transferred to a pediatric clinic 8 days after birth because of suspected Down's syndrome. Oblique palpebral fissures, epicanthic eye-folds, bilateral clinodactyly and slight muscular hypotonia were found.

He was readmitted to the clinic at 3 months of age because of acute bronchopneumonia and acute gastroenteritis.

Physical examination by the author when the patient was 9 months old gave a definite impression of Down's syndrome. Brachycephaly, oblique and narrow palpebral fissures, Brushfield spots, a flat nasal bridge, a high-arched and narrow palate, prominent ears and short fifth fingers with clinodactyly were noted. Syndactyly between the 3rd

and 4th toes of the right foot and between the 4th and 5th toes of the left foot was present. His development has been retarded. He began to sit at 12 months of age and he could not walk or say any single words at 21 months.

Case 52 (21-trisomy plus an extra small metacentric chromosome), a girl born in 1962, is the only child of healthy parents. She was born 2 weeks before term when the mother was 25 and the father 31 years old. Pregnancy and delivery were normal. The mother and maternal grandmother have clinodactyly of the 5th fingers. No other cases of Down's syndrome, malformations or mental retardation had been recorded among the near relatives. The mother had no history of abortions.

Two hours after birth the child had an episode of cyanosis and was transferred to a pediatric clinic where some features suggestive of Down's syndrome were noted. Two days after birth jaundice developed with a maximum total serum bilirubin concentration of 21.5 mg/100 ml on the 4th day. No blood group incompatibility was found and the Coombs test was negative. At 5 months of age she was readmitted to the clinic for evaluation and chromosomal analysis. At that time the features of Down's syndrome were more pronounced. She was brachycephalic and had oblique palpebral fissures, bilateral epicanthus, a flat nasal bridge and a small umbilical hernia. Muscular tone was decreased, and joint hyperflexibility was noted. No signs of congenital heart disease were noted. An ECG was normal. X-ray films showed normal heart and lungs and a normal skull. The pelvis showed changes characteristic of Down's syndrome with a Caffey's index of 56. The second phalanx of the fifth finger was hypoplastic bilaterally.

The blood values were as follows: hemoglobin 12.3 g/100 ml, red-cell count 3.9 millions/cmm, thrombocytes 164,000/cmm and white-cell count 3500/cmm. The differential white-cell count was normal, as well as a bone marrow smear. Urinalyses for protein, abnormal sugars and phenylpyruvic acid were negative. The urinary excretion of amino acids and xanthurenic acid was normal. The serum electrophoretic pattern was normal.

Physical examination by the author when the patient was 11 months of age showed typical features of Down's syndrome. She had a brachycephalic skull, oblique and narrow palpebral fissures, bilateral epicanthus, a flat nasal bridge, a permanently opened mouth with a large and protruding tongue. There was a high-arched and narrow palate, the ears were prominent, and the hands short and broad with atypical four-finger lines. The fifth fingers were short and incurved. There was increased distance between the first and second toes bilaterally. There was a small umbilical hernia. Hyperflexible joints and muscular hypo-

tonia were noted. Development had been retarded. She began to sit and to crawl at 1 year of age. She could not say any single words, stand or walk at 1 9/12 years of age. The karyotypes of the parents are normal.

Case 53 (21-trisomy), a girl, was born in 1961. Her sister, born in 1945, has congenital hypothyroidism. The parents are healthy but the mother has had two previous spontaneous abortions. There are no other cases of Down's syndrome, hypothyroidism, malformations or mental retardation among the near relatives.

The index case was transferred immediately after birth to a pediatric clinic because of suspected Down's syndrome. She was observed to have a flat occiput, oblique palpebral fissures, a flat nasal bridge, a big protruding tongue, short fifth fingers, muscular hypotonia and hyperflexible joints. Physical examination, X-ray films and laboratory tests showed no evidence of congenital heart disease or hypothyroidism.

Physical examination by the author when the girl was 1 6/12 years old showed a typical case of Down's syndrome. The development has been retarded. She began to sit at 16 months and to crawl at 2 years of age. At the present time (age 2 7/12 years) she cannot say any single words or walk.

The mother has a normal karyotype.

Case 54 (21-trisomy), a girl, was born in 1960. The mother had had one previous spontaneous abortion. The patient was admitted to a pediatric clinic at 6 months of age because of retarded development and some features suggestive of Down's syndrome. She was admitted to the clinic again at 8 months of age for chromosomal investigation. At that time physical examination revealed a flat occiput, oblique palpebral fissures, epicanthic eye-fold, a high-arched palate, a big protruding tongue, a flat nasal bridge and short fifth fingers. The muscles were hypotonic and the joints hyperflexible. Physical examination by the author when the patient was 16 months of age showed a girl with definite features of Down's syndrome. In addition to the above findings, Brushfield spots, blepharitis, short broad hands, dry skin and prominent ears were noted. She has had repeated upper respiratory infections and the development has been retarded. She began to sit at 1 8/12 years, but could not walk or talk at 3 years of age.

Case 55 (21-trisomy), a girl (Fig. 30 *c*), was born in 1960. The mother had a subtotal thyroidectomy in 1959 because of thyrotoxicosis and has since then been treated with thyroid extract. The index case was admitted to a pediatric clinic at 5 months of age because of suspected

Down's syndrome. Several features typical of Down's syndrome were noted.

There was no evidence of hypothyroidism. Her development has been retarded. She began to sit at 1 year of age, to walk at 2 6/12 years and to speak single words at 3 1/12 years. A Bühler–Hetzer test at 14 months of age showed a developmental quotient of 66. Physical examination by the author when the patient was 2 6/12 years old showed most of the features characteristic of Down's syndrome. She was also found to have syndactyly between the 2nd and 3rd toes bilaterally.

Case 56 (21-trisomy), a boy, was born 1960. He is the last of four siblings. The oldest sibling has diabetes mellitus. The index case was admitted to a pediatric clinic at 4 months of age because of features suggestive of Down's syndrome. He was found to have a flat occiput, epicanthic eye-folds and slight muscular hypotonia. He was readmitted at 13 months of age for reexamination. At that time typical features of Down's syndrome were noted. A Bühler–Hetzer test showed a developmental quotient of 57. Physical examination by the author when the patient was 2 4/12 years old showed typical features of Down's syndrome. He began to sit at 17 months but could not stand, walk or say any single words at 2 4/12 years of age.

Case 57 (21-trisomy), a girl was born in 1961. The mother had had a legal abortion in 1950. Except for some vaginal bleeding during the third month of gestation the pregnancy was normal. The child was admitted to a pediatric clinic at 2 weeks of age because of jaundice and suspected Down's syndrome. The jaundice, which appeared on the third day after birth, reached its maximum on the 17th day after birth when the total serum bilirubin was 12.9 mg per 100 ml. The child was found to have bilateral epicanthus, slanting palpebral fissures, a flat nasal bridge, muscular hypotonia and hyperflexibility of the joints. Physical examination at 1 4/12 years of age showed a typical case of Down's syndrome with flat occiput, narrow and oblique palpebral fissures, Brushfield spots, epicanthic eye-folds, blepharitis, a flat nasal bridge, abnormal dentition, prominent ears, short and broad hands with atypical four-finger lines, a marked gap between the first and second toes and dry skin. Development has been retarded. He began to sit at 1 year of age and to walk at 2 1/12 years. He could not say any single words at 2 3/12 years of age.

Case 58 (21-trisomy), a girl (Fig. 29 *e*), was born in 1960. She was transferred to a pediatric clinic 2 days after birth because of cyanosis and features suggestive of Down's syndrome. She had slanting palpebral

fissures with slight bilateral epicanthus, an atypical four-finger line on the left hand, marked muscular hypotonia and hyperflexible joints. Examination of the heart showed a probable persistent ostium A–V communis.

Physical examination at 1 year of age showed a girl with marked muscular hypotonia and marked hyperflexibility of the joints. She had slanting palpebral fissures, Brushfield spots, a high-arched and narrow palate and an atypical four-finger line on the right hand. Her height was 75 cm (normal for the age) but the head circumference was only 41.5 cm (normal range for height of 75 cm, 44–49 cm). Development has been retarded. She began to sit at 2 years but could not crawl, stand, walk or say any single words at 2 2/12 years of age. The karyotypes of the parents are normal.

Case 59 (21-trisomy), a girl, was born in 1955. The mother had had 2 previous spontaneous abortions. The index case was transferred from the obstetric ward to a pediatric clinic because of features suggestive of Down's syndrome.

The child was readmitted again at 5 months of age because of feeding difficulties. At that time Down's syndrome was suspected. At five years of age she was admitted to the same clinic because of developmental retardation. A Terman–Merrill test showed an IQ of 51 and her appearance was now strongly suggestive of Down's syndrome. X-ray films showed a normal pelvis.

Physical examination by the author when the patient was 6 10/12 years of age showed a mentally retarded girl with typical Down's syndrome.

Case 60 (21-trisomy), a girl, was born in 1954. The diagnosis of Down's syndrome was made at birth and she has been seen several times at a pediatric clinic. A Terman–Merrill test at 6 years of age showed an IQ of 40.

Case 61 (21-trisomy), a girl, was born in 1961. Immediately after birth she was transferred to a pediatric clinic because of suspected Down's syndrome. Slightly oblique palpebral fissures, slight bilateral epicanthus, a large protruding tongue, a flat nasal bridge, a small umbilical hernia, slight muscular hypotonia and slightly hyperflexible joints were noted. Physical examination by the author when the patient was 12 months old showed a clearcut case of Down's syndrome with several of the characteristic features. Her development has been retarded. She began to sit at 1 3/12 years of age and she could not walk or say any single words at 2 6/12 years.

Case 62 (13–15/21 translocation), a girl, was born in 1962 when the mother was 27 and the father 26 years old. No cases of Down's syndrome or malformations have been recorded among their near relatives

A paternal cousin has given birth to a mentally retarded child. The parents are normal. The mother has been pregnant three times. The first pregnancy resulted in a normal boy and the second terminated in a stillbirth in the 8th month of gestation. No features of Down's syndrome were noted. The propositus was the third pregnancy. Her birth weight was 3120 g, the height was 50 cm, and the head circumference was 34 cm.

Some features suggestive of Down's syndrome were noted at birth. She had a flat occiput, narrow and slanting palpebral fissures, a flat nasal bridge, muscular hypotonia and hyperflexible joints. X-ray films showed hypoplasia of the second phalanx of the fifth fingers. Physical examination by the author when the child was 2 months old showed a clearcut case of Down's syndrome. In addition to the features noted at birth she had slight left-sided epicanthus, Brushfield spots, permanently opened mouth, high-arched and narrow palate, a small umbilical hernia and increased distance between the first and second toes bilaterally. Her development has been retarded. She began to sit and crawl at 9 months but could not stand, walk or say any single words at 1 7/12 years of age.

Case 63 (21-trisomy), a girl, was born in 1962. A distant relative of the mother gave birth to a girl with Down's syndrome at the age of 41 years.

The index case was transferred to a pediatric clinic 6 days after birth because of features suggestive of Down's syndrome. Physical examination by the author when the patient was 13 days old showed several features characteristic of Down's syndrome. Examination at 1 9/12 years of age showed a definite case of Down's syndrome with retarded development.

Case 64 (21-trisomy), a boy, was born in 1962. He was transferred from the obstetrical ward to a pediatric clinic because of Down's syndrome. Cardiac examination revealed a harsh systolic murmur. He developed neonatal jaundice with a maximum total serum bilirubin concentration of 17.0 mg/100 ml on the 4th day after birth. Subsequently, because of congestive heart failure, digitalis therapy was begun. His development had been retarded. He could not roll over when placed on his back, sit with support, creep or imitate sounds at 12 months of age. He died at the age of 12 months after an upper respiratory infection.

Case 65 (21-trisomy), a boy, was born in 1962. He was admitted to a pediatric clinic at the age of six weeks because of features suggestive of Down's syndrome. Physical examination by the author when the patient was 8 months old showed characteristic features of Down's syndrome. Development has been retarded. He could not sit, creep, walk or say any single words at 1 7/12 years of age.

Case 66 (21-trisomy), a girl, was born in 1962. She was transferred from the obstetric ward to a pediatric clinic because of features suggestive of Down's syndrome. Physical examination by the author when the patient was 5 months old showed definite features of Down's syndrome. Development has been retarded. She began to sit at 1 2/12 years, and could not stand, walk or say any single words at 1 8/12 years of age.

Case 67 (21-trisomy), a girl, was born in 1962. The mother had had one previous spontaneous abortion. Down's syndrome was diagnosed shortly after birth at a pediatric clinic. She began to sit at 1 2/12 years and could not creep, walk or say any single words at 1 6/12 years of age.

Case 68 (21-trisomy), a girl, was born in 1961. She has a normal brother born in 1960.

Her mother, maternal grandmother and a maternal aunt have short and slightly incurved fifth fingers. She was admitted to a pediatric clinic at 11 months of age because of retarded development and some features suggestive of Down's syndrome.

She was noted to have slight hypertelorism, epicanthic eye-folds, slightly hyperflexible joints of the fingers, short thumbs, short and slightly incurved fifth fingers and a bilateral four-finger line. X-ray films of the skull and pelvis were normal (Caffey's index 77). Ossification centers were normal for the age. X-ray examination of the hands showed short phalanges of the thumbs and hypoplasia of the 2nd phalanx of the fifth fingers.

Physical examination by the author when the index case was 1 4/12 years old showed a girl with Down's syndrome.

Her development has been retarded. She began to sit at 10 months, to creep at 1 1/12 years, to walk at 1 10/12 years and could not say any single words at 2 6/12 years of age. The karyotypes of the parents are normal.

Case 69 (21-trisomy), a boy, was born in 1956. The mother, who has had a cleft palate repaired; the maternal grandfather; two maternal aunts and two maternal uncles have syndactyly of the second and third toes bilaterally.

The index case was transferred to a pediatric clinic at one day of age because of slight cyanosis and features suggestive of Down's syndrome. He had marked muscular hypotonia, a high-arched and narrow palate, a four-finger line on the left hand, epicanthic eye-folds, slanting palpebral fissures, Brushfield spots, micrognathia, a small mouth and prominent ears. Postnatal jaundice developed with a maximum total serum bilirubin concentration of 24 mg/100 ml on the fourth day after birth.

His development has been clearly retarded and he was readmitted to the clinic at 6 4/12 years of age because of suspected Down's syndrome and for developmental testing. At that time he had many of the features characteristic of Down's syndrome. He also had slight bilateral ptosis, a small mouth, micrognathia, syndactyly of the 2nd and 3rd toes bilaterally, funnel chest and underdeveloped musculature. X-ray films of the hands and pelvis were normal.

A Terman–Merrill test revealed an IQ of 30–35.

Case 70 (21-trisomy), a boy with Down's syndrome, was born in 1954. Up to 4 years of age he had been admitted 4 times to a pediatric clinic because of respiratory infections and a congenital heart defect. Features suggestive of Down's syndrome and bilateral syndactyly between the 2nd and 3rd toes were noted.

In 1961 he was operated upon because of a ventricular septal defect. At that time he was regarded as a characteristic case of Down's syndrome. A Terman–Merrill test in 1960 showed an IQ of 63.

Case 71 (21-trisomy), a girl with typical Down's syndrome, was born in 1947. A Terman–Merrill test in 1957 showed an IQ of 29.

Case 72 (21-trisomy), a boy, was born in 1946. In addition to typical features of Down's syndrome there was retroposition of the 4th toes. A Terman–Merrill test in 1956 gave an IQ of 33.

Case 73 (21-trisomy), a boy, with typical Down's syndrome was born in 1946. A Terman–Merrill test in 1954 gave an IQ of 31.

Case 74 (21-trisomy), a girl, was born in 1962. She was transferred to a pediatric clinic immediately after birth because of typical features of Down's syndrome including a congenital heart defect. The diagnosis of Down's syndrome was confirmed. X-ray films of the chest showed dilatation of the heart. The child was readmitted at 4 months of age because of cardiac decompensation. A probable ventricular septal defect was diagnosed and digitalis therapy was begun. She died at 4 1/2 months of age.

Case 75 (21-trisomy), a boy, was born in 1962. The mother had had one previous spontaneous abortion. He was transferred from the obstetrical ward to a pediatric clinic because of feeding difficulties and features suggestive of Down's syndrome. He was found to have micrognathia.

Physical examination by the author when the patient was 8 months old showed a definite case of Down's syndrome. Development has been retarded. He began to sit at 11 months but could not creep, stand or say any single words at 16 months of age.

Case 76 (21-trisomy), a female with typical Down's syndrome, was born in 1929. A Terman–Merrill test in 1958 gave an IQ of 42.

Case 77 (21-trisomy), a female with typical Down's syndrome, was born in 1950. She has bilateral retroposition of the 4th toe. A Terman–Merrill test in 1955 gave an IQ of 44.

Case 78 (21-trisomy), a male with typical Down's syndrome, was born in 1944. His mother had had one previous spontaneous abortion. He has syndactyly between the 4th and 5th toes bilaterally. A Terman–Merrill test in 1957 gave an IQ of 38.

Case 79 (21-trisomy), a male with typical Down's syndrome, was born in 1941. He has bilateral radio-ulnar synostosis and congenital heart failure. He is markedly mentally retarded and lives in an institution for mental defectives.

Case 80 (21-trisomy), a male, was born in 1909. In addition to typical signs of Down's syndrome there are features of Klinefelter's syndrome including gynecomastia; small, soft testes; absence of axillary hair; and scanty pubic and facial hair. He has broad hips and a high-pitched voice. A Terman–Merrill test in 1961 showed an IQ less than 30.

Case 81 (21-trisomy), a female with typical Down's syndrome, was born in 1944 when the mother was 24 years old. Congenital heart disease is present. A Terman–Merrill test in 1956 gave an IQ of 31. The father died at the age of 42 of alcoholic cirrhosis. The mother, who is normal and healthy, has had two pregnancies. The second pregnancy resulted in a mentally retarded and autistic boy with microcephaly, epilepsy and slightly increased muscular tone (Case 81 Br, Fig. 31 *c*). He was born when the mother was 27 years old and was found to have an extra small metacentric chromosome (Fig. 28). The karyotype of the mother is normal. No instances of Down's syndrome, congenital malformations

or mental retardation have been recorded among the near relatives of the parents. These patients will be described in detail elsewhere (Gustavson *et al.*, 1964 *b*).

Case 82 (21-trisomy), a girl with typical Down's syndrome (Fig. 30 *b*), was born in 1948. She lives in an institution for mental defectives. The mother had had a legal abortion in 1945.

Case 83 (21-trisomy), a girl, was born in 1962. When she was 3 days old she was admitted to a pediatric clinic because of Down's syndrome and neonatal jaundice with a maximum total serum bilirubin concentration of 23.1 mg/100 ml on the day of admission. Subluxation of the left hip was noted. Her development has been retarded. She could not sit, creep, stand or say any single words at 1 4/12 years of age.

Case 84 (21-trisomy), a female with typical Down's syndrome, was born in 1921. She has bilateral retroposition of the 4th toe. A Terman–Merrill test in 1952 gave an IQ of 19.

Case 85 (21-trisomy) was a female with typical Down's syndrome born in 1935. She died in 1962. The autopsy diagnoses were Down's syndrome, persistent ostium A–V communis and abscess of the brain.

Case 86 (21-trisomy), a boy with typical Down's syndrome, was born in 1941. A diagnosis of diabetes mellitus was made in 1961. A Terman–Merrill test in 1955 gave an IQ of 25.

Case 87 (21-trisomy), a female with typical Down's syndrome, was born in 1940. The mother had had vaginal bleeding during the 3rd and 5th months of gestation. A Terman–Merrill test in 1955 gave an IQ of 21.

Case 88 (21/21–22 translocation or isochromosome long arm 21), a female with typical Down's syndrome, was born in 1939 when the parents were 24 years old. No instances of Down's syndrome, congenital malformations or mental retardation have been recorded among their near relatives. The parents are normal and healthy. The mother has had two pregnancies. The second child is a normal male born in 1943. X-ray films of the pelvis were normal. A Terman–Merrill test in 1959 gave an IQ of 21. The karyotypes of the parents are normal.

Case 89 (21-trisomy), a male with typical Down's syndrome, was born in 1945. A developmental test (Bühler–Hetzer) in 1954 gave a quotient of 29.

Case 90 (21-trisomy), a boy, was born in 1963. He was admitted to a pediatric clinic immediately after birth because of typical Down's syndrome.

He died of bronchopneumonia at 2 1/2 months of age. The autopsy diagnoses were Down's syndrome and bronchopneumonia. The heart was normal.

Case 91 (21-trisomy), a female with typical Down's syndrome, was born in 1942. She has a congenital heart defect. A Terman–Merrill test in 1947 gave an IQ of 30.

Case 92 (21-trisomy), is a female born in 1938 with typical Down's syndrome. A Terman–Merrill test in 1947 gave an IQ of 30.

Case 93 (21-trisomy), is a girl with typical Down's syndrome born in 1947. The mother had had vaginal bleeding during the second month of gestation. A Terman–Merrill test in 1957 gave an IQ of 57.

Case 94 (21-trisomy), a girl, was born in 1963. Features suggestive of Down's syndrome were noted at birth. She was transferred to a pediatric surgery clinic two days after birth for operative repair of anal atresia.

Her development seems to have been retarded. She could not creep, sit, stand or speak any single words at 13 months of age.

Case 95 (21-trisomy), a boy, was born in 1962. He was admitted to a pediatric clinic immediately after birth because of features suggestive of Down's syndrome.

He was found to have congenital heart disease with a probable ventricular septal defect. The development has been retarded. He could not sit, creep, stand or speak any single words at 1 2/12 years of age.

Case 96 (21-trisomy), a boy, was born in 1963. He was transferred from the obstetric ward to a pediatric clinic because of features characteristic of Down's syndrome.

He failed to thrive and died at the age of 3 months after episodes of vomiting and diarrhea. The autopsy diagnosis was Down's syndrome.

Case 97 (21-trisomy), a girl, was born in 1963. She was transferred from the obstetric ward to a pediatric clinic because of features characteristic of Down's syndrome. Her development has been retarded.

Case 98 (21-trisomy), a boy with typical Down's syndrome, was born in 1957. His development has been retarded. He began to sit at 1 2/12 years of age, to walk at 2 years and could only say a few simple words

at 6 years of age. The mother has had three pregnancies. The first resulted in a normal girl, the second in the index case and the third in a normal boy (Case 98 Br) who developed blast cell leukemia at 2 11/12 years of age. He was treated with 6-Mercaptopurine until his death at 4 5/12 years of age. Chromosomal analyses of cultured cells from bone marrow and blood of case 98 Br at 4 1/12 years of age showed chromatid breaks in 11 per cent of the cells. No other abnormalities were noted in the karyotype. The karyotypes of the parents are normal.

Case 99 (21-trisomy), a girl with typical Down's syndrome, was born in 1959. Her development has been retarded. She began to sit at 9 months, to walk at 1 8/12 years and could only say a few simple words at 3 10/12 years of age. The mother has had three pregnancies. The first resulted in a stillbirth in the 7th month, the second in a normal boy and the third in the index case. The karyotypes of the parents are normal. A paternal uncle of the index case has Down's syndrome (Case 103).

Case 100 (21-trisomy), a female with typical Down's syndrome, was born in 1917. A Terman–Merrill test in 1957 gave an IQ of 51.

Case 101 (21-trisomy), a female with typical Down's syndrome, was born in 1942. She has syndactyly of the 2nd and 3rd toes bilaterally. A Terman–Merrill test in 1959 gave an IQ of 34.

Case 102 (21/21–22 translocation or isochromosome long arm 21), was a boy born in 1963 when the mother was 36 and the father 50 years old. He was admitted to a pediatric clinic immediately after birth because of suspected Down's syndrome. He developed neonatal jaundice with a maximum total serum bilirubin concentration of 16 mg/100 ml on the third day after birth. X-ray films showed hypoplasia of the middle phalanx of the fifth fingers. Caffey's index was 61, a value typical of Down's syndrome. He was readmitted to the clinic at the age of one month because of acute gastroenteritis. At that time he showed definite features of Down's syndrome. He expired on the third day after admission. The autopsy diagnoses were Down's syndrome and acute gastroenteritis.

The mother had one pregnancy in a previous marriage. The child was a normal girl. The index case was the mother's only pregnancy of her second marriage. The father, who had three normal children in a previous marriage, has short stature, prominent ears and short fifth fingers. The first child, a daughter, died of acute leukemia when she was 16 years old. The third child, a boy, has a four-finger line on the left palm. The karyotypes of the parents are normal.

Case 103 (21-trisomy) is a male with typical Down's syndrome, born in 1938. He has a niece with Down's syndrome, Case 99 (21-trisomy). He lives in an institution for mental defectives.

Case S 1 (Normal karyotype), a boy (Fig. 32 *a–d*), was born in 1958. He is the only child of healthy parents. A diagnosis of chondrodystrophia congenita punctata with typical skeletal X-ray changes was made at a pediatric clinic immediately after birth. Caffey's index was 52. In addition to chondrodystrophia congenita punctata Down's syndrome was suspected. He had brachycephaly, slanting palpebral fissures, a flat nasal bridge, protruding tongue, a four-finger line on each palm, incurved fifth fingers, muscular hypotonia and hyperflexible joints. Chromosomal investigation was made at 9 months of age.

A Gesell test at 13 months of age showed motor and language development corresponding to 9 months. A Merrill–Palmer test at 2 6/12 years of age gave an IQ of 90. Physical examination by the author when the patient was 4 years old showed a chondrodystrophic boy with short extremities, slightly prominent forehead, slanting palpebral fissures, depressed nasal bridge, protruding tongue, bilateral four-finger lines, incurved fifth fingers and funnel breast. He had muscular hypotonia, hyperflexible joints and a waddling gait. A diagnosis of Down's syndrome could not be made. He was a case of chondrodystrophia congenita punctata with a normal mental development.

Case S 2 (Normal karyotype), a male (Fig. 32 *e*), was born in 1932. He has congenital deafness and marked mental retardation. He has lived in institutions for mental defectives since 4 years of age. An atypical form of Down's syndrome has been suspected.

Physical examination by the author showed short stature; low hair line; bilateral epicanthus; short and incurved fifth fingers; pronounced gap between the 1st and 2nd toes; and undescended testes.

This patient had only 2 of Øster's 10 cardinal signs characteristic of Down's syndrome (Øster, 1953) and the palm prints were not indicative of this syndrome. His appearance was not that of Down's syndrome.

Case S 3 (Normal karyotype), a boy (Fig. 32 *f*), was born in 1959. A sister born in 1947 is mentally retarded because of brain damage at birth. He was admitted to a pediatric clinic at 3 1/2 months of age because of retarded development, some features suggestive of Down's syndrome and repeated upper respiratory infections. He had bilateral epicanthus, a flat nasal bridge, slight ptosis of the eye-lids, umbilical hernia, four-finger line on the right palm and retroposition of the 4th toes. Chromosomal investigation was made at 4 months of age.

Since 1 year of age he has been readmitted several times for follow-up studies. The diagnoses were unspecified mental deficiency, asthmatic bronchitis and ectopic left kidney. He was no longer suspected to have Down's syndrome. A Gesell test at 2 3/12 years of age showed a development equivalent to that of a child of 1 2/12–1 6/12 years. The patient had only 2 of Øster's cardinal signs, and his appearance was not that of Down's syndrome.

Case S 4 (Normal karyotype), a girl, was born in 1959. She was admitted to a pediatric clinic at 11 months of age because of retarded development and some features suggestive of Down's syndrome. She had a flat occiput, slanting palpebral fissures, incurved fifth fingers, dry skin and slightly decreased muscular tonus. A Gesell test showed slightly retarded development. A chromosomal analysis was made at 11 months of age.

She was seen again at the age of 2 9/12 years. The impression at that time was that she did not have Down's syndrome. A Gesell test at 2 10/12 years of age showed motor and adaptive behaviour development equivalent to 2 6/12 years and language development equivalent to 2 years. This development is only mildly depressed and is not the degree of retardation accompanying Down's syndrome. Seen by the author at the age of 3 5/12 years her development appeared to fall within the normal range and her appearance was not that of Down's syndrome.

Case S 5 (Normal karyotype), a boy (Fig. 33 *a*), was born in 1953. He was admitted to a children's psychiatric clinic at 6 9/12 years of age because of retarded development. A Terman–Merrill test gave an IQ of 46. X-ray films of the skeleton were normal.

Physical examination showed Brushfield spots, a flat nasal bridge, clinodactyly and prominent ears.

Physical examination of the index case at 8 10/12 years of age by the author showed no evidence of Down's syndrome. The palm prints were not indicative of Down's syndrome. He did not have any of the diagnostic cardinal signs stated by Øster and his appearance was not that of the syndrome.

Case S 6 (Normal karyotype), a girl (Fig. 33 *b*), was born in 1961. She was referred to a pediatric clinic immediately after birth because of prematurity. She was found to have some features suggestive of Down's syndrome such as oblique palpebral fissures, a flat nasal bridge, a somewhat large and extended tongue and a high-arched palate. Congenital heart disease with a probable ventricular septal defect was diagnosed. A chromosomal analysis was made at that time. Her develop-

ment has been normal. She began to sit at 7 months, to walk at 15 months, to speak single words at 10 months and short sentences at 18 months af age. She was seen by the author for the second time when she was 2 8/12 years old. At that time a diagnosis of Down's syndrome could not be made. Her palm prints were not suggestive and only 2 of Øster's cardinal signs, brachycephaly and oblique palpebral fissures were found.

Case S 7 (Normal karyotype), a male (Fig. 33 *c*), was born in 1949. He has lived in an institution for mental defectives since 1953. A Bühler–Hetzer test at 6 years of age gave a developmental quotient of 31. His diagnosis has been mental retardation of unknown etiology. He also shows some features slightly suggestive of Down's syndrome such as brachycephaly, short fifth fingers and increased distance between the first and second toes bilaterally. A chromosomal analysis was made in 1961. Physical examination by the author when the patient was 12 8/12 years old showed no evidence of Down's syndrome. He had only one of Øster's cardinal signs for the diagnosis of Down's syndrome (brachycephaly) and his palm prints were normal.

Case S 8 (Normal karyotype), a male (Fig. 33 *d*), was born in 1944. Since 1953 he has periodically been in institutions for mental defectives. He had frequent upper respiratory infections. The diagnosis was mental retardation with some features suggestive of Down's syndrome.

In 1959 he was admitted to a psychiatric ward. He was found to have some features often found in Down's syndrome: a four-finger line bilaterally, short and incurved fifth fingers and increased distance between the 1st and 2nd toes bilaterally. A Terman–Merrill test at 15 10/12 years of age gave an IQ of 42.

A physical examination of the index case was performed by the author when the patient was 18 years old. It was the author's impression that the patient was not a case of Down's syndrome. He had only 2 of Øster's cardinal signs for a diagnosis of Down's syndrome and his appearance was not that of the syndrome.

Case S 9 (Normal karyotype), a girl (Fig. 33 *e*), was born in 1959. She was transferred from the obstetrical ward to a pediatric clinic because of cyanosis immediately after birth.

She was seen at 5 and again at 12 months of age because of retarded development. Some features often found in Down's syndrome were observed. She had brachycephaly, flat nasal bridge, a four-finger line of the left palm, muscular hypotonia and hyperflexible joints. An EEG was normal. A chromosomal analysis was made at 2 years of age. Her

development has been retarded. She began to sit at 1 6/12 years but could not creep, stand, walk or talk at 3 6/12 years of age. Physical examination by the author when the patient was 2 10/12 years old revealed a mentally retarded girl with only two of Øster's cardinal signs, and the palm prints were not indicative of Down's syndrome.

Case S 10 (Normal karyotype), a girl, was born in 1954. She was cyanotic during the first 12 hours after birth. The patient was referred to a children's psychiatric clinic at 7 years of age because of retarded development. A Terman–Merrill test gave an IQ of 76. She was noted to have some features suggestive of Down's syndrome so that a chromosomal analysis was made. She had oblique palpebral fissures, a flat nasal bridge, an atypical four-finger line on the right palm, increased distance between the first and second toes bilaterally and muscular hypotonia. The head circumference was less than normal. X-ray films of the pelvis were normal.

It was the author's impression that the patient was not a case of Down's syndrome. She had only 2 of Øster's cardinal signs and her palm prints were not indicative of Down's syndrome.

Case S 11 (Normal karyotype), a girl (Fig. 33 *f*), was born in 1957. The mother had had 2 previous spontaneous abortions. The index case had convulsions three times between 3 and 3 6/12 years of age. No cause of the convulsions was found.

She was admitted to a children's psychiatric clinic at 4 9/12 years of age because of retarded development. Some features suggestive of Down's syndrome were noted and a chromosomal investigation was made. Her height and head circumference were below normal for the age. She had irregular alignment of the teeth, a narrow palate, short fifth fingers, syndactyly of the 3rd and 4th toes of the right foot, hyperflexible joints and muscular hypotonia. X-ray films of the pelvis were normal. Bühler–Hetzer and Gesell tests showed a development equivalent to that of child 1 to 2 years old. No cause of her retarded development was found. It was the author's impression that the patient was not a case of Down's syndrome. She had only 2 of Øster's cardinal signs and her palm prints were not indicative of Down's syndrome.

Case S 12 (Normal karyotype), a girl, was born in 1962. The mother had had two previous spontaneous abortions. After birth the index case was immediately transferred to a pediatric clinic because of feeding difficulties and some features suggestive of Down's syndrome. She had slightly oblique palpebral fissures, a flat nasal bridge, great laxity of the skin of the neck and muscular hypotonia. A chromosomal investigation was made.

Physical examination by the author when the patient was 5 months old showed a normally developed girl with slightly oblique palpebral fissures and a somewhat flat nasal bridge. Her palm prints were normal. A diagnosis of Down's syndrome could not be made. Her development has continued in a normal fashion. She began to sit at 6 months, to stand at 11 months, to walk at 13 months and could say a few simple words at 12 months of age.

Case S 13 (Normal karyotype), a boy (Fig. 34 *c, d*), was born in 1960. He was transferred to a pediatric clinic immediately after birth because of cyanosis. Physical examination showed slanting palpebral fissures, epicanthic eye-folds, hypertelorism, a large and protruding tongue, laxity of the skin of the neck, an atypical four-finger line on the right palm and marked enlargement of the liver and spleen. X-ray films of the skeleton were normal. Karyotyping was made at 8 months of age because of a slight suspicion of Down's syndrome. He has since been admitted three times to a pediatric clinic, the last time at 3 3/12 years of age. In addition to the findings noted at birth an enlarged head, asymmetrical pupils, a flat nasal bridge, bilateral inguinal hernias, and decreased muscular tonus were noted. The epicanthic eye-folds and the protruding tongue were no longer present. There was a marked urinary excretion of mucopolysaccharides. He was regarded to have an atypical form of gargoylism. His development has been somewhat retarded. A Bühler–Hetzer test at 3 3/12 years of age gave a development quotient of 79.

The general appearance of the patient, with hypertelorism, marked liver and spleen enlargement and the fact that the palm prints and skeletal X-ray findings were not indicative of Down's syndrome, gave the author the impression that this was not a case of Down's syndrome. The most probable diagnosis seems to be an atypical form of gargoylism.

Case S 14 (Normal karyotype), a girl (Fig. 34 *a*), was born in 1953. She was admitted to a children's psychiatric clinic at 7 11/12 years of age because of retarded development. She was found to have some features often found in Down's syndrome, such as epicanthic eye-folds, four-finger line on the left palm, permanently open mouth, and increased distance between the first and second toes bilaterally. The fourth and fifth fingers were incurved bilaterally.

She had a probable ventricular septal defect and a tendency to adult type of fat distribution. X-ray films of the skeleton were normal.

A Terman–Merrill test gave an IQ of 53. No cause of her mental

retardation was found. She was discharged with the diagnoses of feeble-mindedness and encephalopathy.

Her palm prints were not indicative of Down's syndrome. She had only two of Øster's cardinal signs and the appearance was not that of Down's syndrome. In the author's opinion she was not a case of Down's syndrome.

Case S 15 (Normal karyotype), a girl (Fig. 34 *e, f*), was born in 1960. She was admitted to a pediatric clinic at 2 1/2 months of age because of feeding difficulties. She was found to have some features slightly suggestive of Down's syndrome such as a flat occiput and probably retarded development.

Subsequently, she has been readmitted several times because of respiratory infections, convulsions and retarded development. Pneumoencephalography at 1 5/12 years of age showed dilatation of the ventricular system with symmetrical atrophy of the brain. Repeated EEG-examinations have shown marked epileptogenic activity.

A Gesell test at 3 2/12 years of age showed a motor development equivalent to a child of 15 months, adaptive behaviour and language development equivalent to 8–10 months. The diagnoses at that time were atrophy of the brain with mental deficiency and epilepsy. A diagnosis of Down's syndrome could not be made.

Physical examination by the author when the patient was 2 years old showed a mentally retarded girl with flat occiput and Brushfield spots. The palm prints were not typical of Down's syndrome. It was the author's opinion that this child was not a case of Down's syndrome.

Case S 16 (Normal karyotype), a boy (Fig. 34 *b*), was born in 1955. He had a cleft palate repaired in 1957. He lives in an institution for mental defectives and was admitted to a pediatric clinic in 1962 when he was classified as an idiot with some features suggestive of Down's syndrome. A flat occiput, a broad nasal bridge, hyperflexible joints and muscular hypotonia were found.

Only the right testis was descended. He was markedly mentally retarded and did not understand when spoken to. He could not talk or eat without help and had fecal and urinary incontinence.

Karyotyping was done because of a slight suspicion of an atypical form of Down's syndrome.

The height was normal for his age. He had only a few of the signs regarded as characteristic of Down's syndrome and his appearance was not that of Down's syndrome.

Fig. 29 *a*. Case 12 at 1 month of age.
Fig. 29 *b*. Case 25 at 1 month of age.
Fig. 29 *c*. Case 20 at the age of 3 days.
Fig. 29 *d*. Case 27 at the age of 1 day.
Fig. 29 *e*. Case 58 at the age of 4 days.
Fig. 29 *f*. Case 6 at 4 years of age.

Fig. 30 *a*. Case 42 at 13 years of age.
Fig. 30 *b*. Case 82 at 15 years of age.
Fig. 30 *c*. Case 55 at 2 years and 6 months of age.
Fig. 30 *d*. Case 44 at 2 years and 9 months of age.
Fig. 30 *e*. Case 13 at 13 months of age
Fig. 30 *f*. Case 34 at 12 months of age.

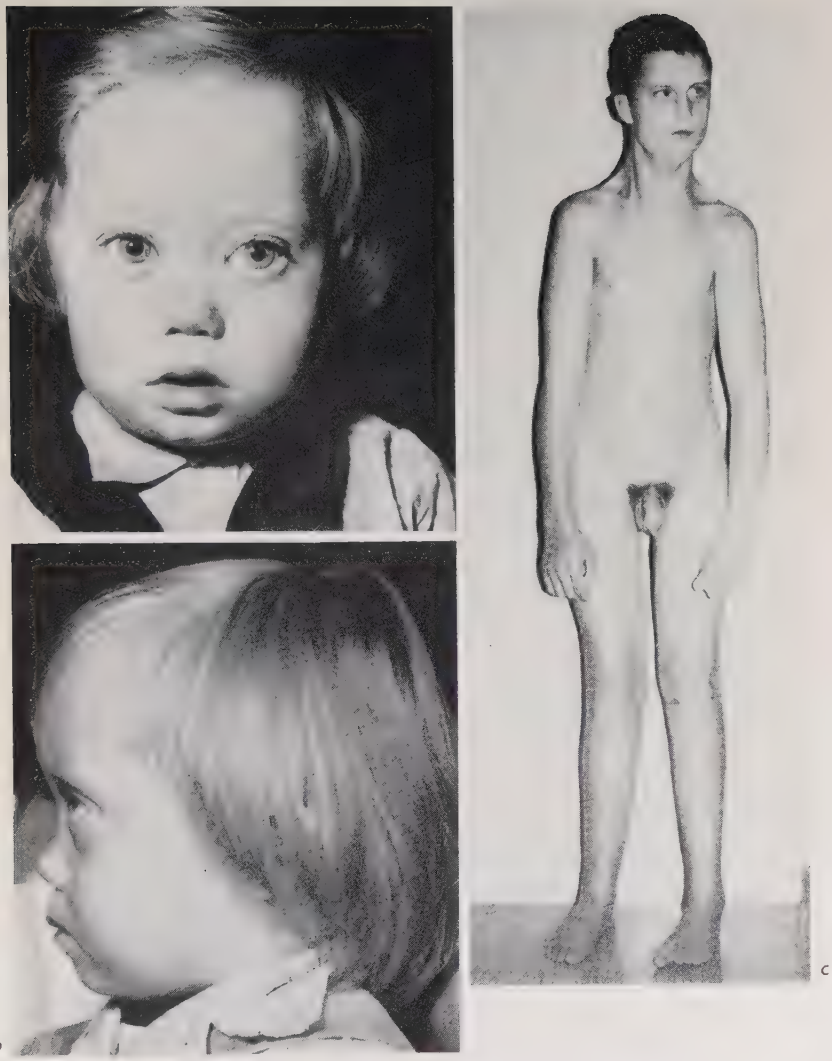


Fig. 31 *a*. Case 45 at 1 year and 5 months of age.
Fig. 31 *b*. Case 45 at 2 years and 4 months of age
Fig. 31 *c*. Case 81 Br at 16 years of age.

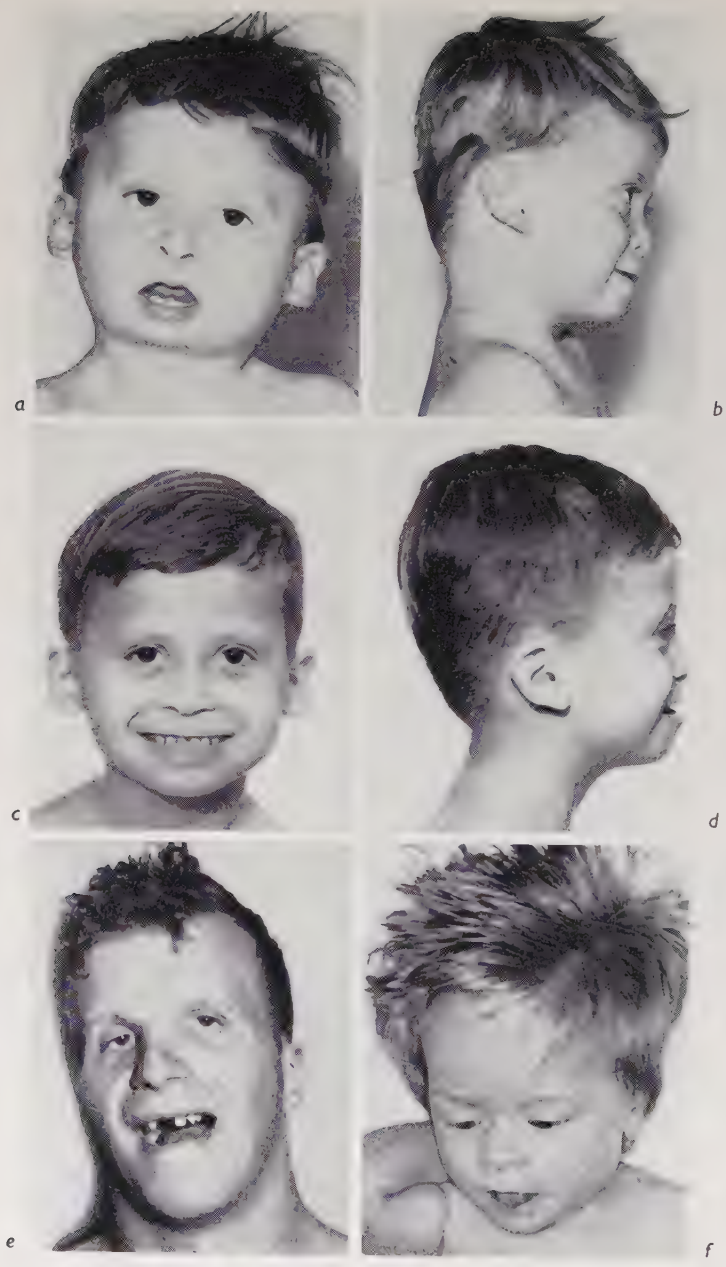


Fig. 32 *a* and *b*. Case S 1 at 13 months of age.
Fig. 32 *c* and *d*. Case S 1 at 4 years of age.
Fig. 32 *e*. Case S 2 at 28 years of age.
Fig. 32 *f*. Case S 3 at 4 months of age.

Fig. 33 *a*. Case S 5 at 9 years of age.
Fig. 33 *b*. Case S 6 at 1 month of age.
Fig. 33 *c*. Case S 7 at 12 years of age.
Fig. 33 *d*. Case S 8 at 15 years of age.
Fig. 33 *e*. Case S 9 at 1 year and 5 months of age.
Fig. 33 *f*. Case S 11 at 5 years of age.

Fig. 34 *a*. Case S 14 at 8 years of age.
Fig. 34 *b*. Case S 16 at 8 years of age.
Fig. 34 *c*. Case S 13 at the age of 3 days.
Fig. 34 *d*. Case S 13 at the age of 1 year and 6 months.
Fig. 34 *e*. Case S 15 at 3 months of age.
Fig. 34 *f*. Case S 15 at 1 year and 6 months of age.

Tables I–V

Explanation of Symbols in Appendix Tables I–III

Mo = mother
Fa = father
Br = brother
Si = sister
Sk = cultured skin cells
BM = cultured bone marrow cells
Or = oral mucosa cells
* = 4 chromosomes in group 21–22
= trisomy for a small acrocentric chromosome

Unless otherwise noted in the karyotype interpretation the cells with 47 chromosomes were trisomic for a small acrocentric chromosome.

Explanations of Symbols in Appendix Tables IV and V

The author has personally examined 111 of the 119 individuals listed in Tables IV and V. Cases 5, 9, 15, 23, 37, 74, 85 and 90 in Table IV were not examined by the author. The data of these 8 patients have been taken from their hospital records.

\+ = present
– = absent
(+) = unilateral
⊀ = flat occiput (specific measurements lacking)
T = typical Down's syndrome
S = suspected Down's syndrome
F = familial Down's syndrome
Y = child with Down's syndrome born to young mother

TABLE I. *Cytogenetical data of the patients with Down's syndrome or suspected Down's syndrome who were found to have chromosomal aberrations (Cases 1–103).*

Case number	Age at the time of chromosome investigation, years	Type of tissue cultured	No. of cells with chromosome count: <45	45	46	47	48	Total number of counted and analysed cells	Karyotype interpretation	Sex chromatin
1	10 6/12	Bone marrow		2+	2+	35	1+	40	21-trisomy	
2	18 10/12	Bone marrow				6		6	21-trisomy	
2		Skin		1	1+	20		22	21-trisomy	
3	29 10/12	Skin		1		16		17	21-trisomy	
4	4/12	Bone marrow				10		10	21-trisomy	
5	<1/12	Skin				6	1+	7	21-trisomy	
5		Kidney			1+	15		16	21-trisomy	
6	3 2/12	Skin I		2	24			26	Monosomic 16	
6		Skin II			16			16	trisomic 21 or 22?	54 % (Sk)
6		Bone marrow		1	13	1		15	Deletion or translocation involving 16?	56 % (Or)
6 Mo	30 10/12	Skin		2*	18			20	Normal	
6 Fa	35 0/12	Skin		1*	19			20	Normal	
7	9 7/12	Bone marrow				18		18	21-trisomy	Neg. (BM)
8	4/12	Skin				16		16	21-trisomy	Neg. (Sk)
8 Mo	23 6/12	Skin	1		11			12	Normal	
8 Fa	24 10/12	Skin			14			14	Normal	
9	1/12	Bone marrow				13		13	21-trisomy	Neg. (BM)
9 Mo	26 5/12	Bone marrow		1*	11			12	Normal	
9 Fa	25 6/12	Bone marrow			12			12	Normal	

10	2	6/12	Bone marrow			4		4	21-trisomy	
10			Skin			8		8	21-trisomy	
11		< 1/12	Bone marrow			14		14	21-trisomy	
11 Mo	38	7/12	Skin	10				10	Normal	
11 Fa	32	9/12	Skin	12				12	Normal	
12		1/12	Skin			24		24	21-trisomy	Neg. (BM)
13		< 1/12	Bone marrow			7		7	21-trisomy	
14		10/12	Bone marrow			12		12	21-trisomy	
15		7/12	Bone marrow			15		15	21-trisomy	
16		9/12	Skin I	1+	4			5	21-trisomy	
16			Skin II			15		15	21-trisomy	
17		1/12	Skin			12		12	21-trisomy	
18		< 1/12	Skin			11		11	21-trisomy	
19	1	0/12	Skin			10		10	21-trisomy	
20		< 1/12	Skin			10		10	21-trisomy	
21		1/12	Skin			10		10	21-trisomy	Neg. (Sk)
22		< 1/12	Skin			11		11	21-trisomy	
23		1/12	Skin			11		11	21-trisomy	46 % (Sk)
24	7	0/12	Skin			15		15	21-trisomy	32 % (Or)
25		< 1/12	Skin	1+	18			19	21-trisomy	Neg. (Sk)
26		3/12	Skin			12		12	21-trisomy	
27		< 1/12	Skin			19		19	21-trisomy	
28	15	4/12	Blood			10		10	21-trisomy	Neg. (Sk)
28			Skin	1+	37			38	21-trisomy	
28 Mo	46	8/12	Blood	15				15	Normal	
28 Fa	46	5/12	Blood	15				15	Normal	
29	11	7/12	Blood			40		40	21-trisomy	Neg. (Sk)
29			Skin I	5	18	20		43	46/47/48	
29			Skin II	10	8	7		25	mosaicism	
29 Mo	35	7/12	Skin	19				19	Normal	

Table I (*continued*)

Case number	Age at the time of chromosome investigation, years	Type of tissue cultured	No. of cells with chromosome count: <45	45	46	47	48	Total number of counted and analysed cells	Karyotype interpretation	Sex chromatin
29 Fa	34 8/12	Blood		1*	20			21	Normal	
30	24 6/12	Skin		1+	1+	40		42	21-trisomy	40 % (Sk)
30 Mo	65 9/12	Blood			35			35	Normal	
30 Fa	66 4/12	Blood		1*	34			35	Normal	
31 sibs	22 1/12	Skin			2+	47		49	21-trisomy	Neg. (Sk)
32 sibs	20 6/12	Blood				29		29	21-trisomy	36 % (Or)
31–32 Mo	63 10/12	Blood	1*	2*	31			34	Normal	
31–32 Fa	55 11/12	Blood			20			20	Normal	
33	6 6/12	Skin				25		25	21-trisomy	22 % (Or)
34	6/12	Bone marrow		1	18	1		20	21/21–22	49 % (Sk)
34		Skin		2	86	2		90	translocation or isochromosome 21	53 % (Or)
34 Mo	31 3/12	Blood		1*	13	1*		15	Normal	
34 Fa	40 7/12	Blood		1*	14			15	Normal	
34 Br	2 7/12	Skin		1*	63			64	Normal	
35	1/12	Skin			1+	30		31	21-trisomy	40 % (Sk)
36	8/12	Skin				16		16	21-trisomy	
37	2/12	Skin				26		26	21-trisomy	
38	3/12	Skin				18		18	21-trisomy	33 % (Or)
39 sibs	13 11/12	Blood				38		38	21-trisomy	Neg. (Or)
40 sibs	12 4/12	Blood			2+	29		31	21-trisomy	26 % (Or)
39–40 Mo	36 10/12	Blood		1*	79	1*		81	Normal	

39–40 Fa	42	11/12	Blood			31				31	Normal	
41	14	6/12	Skin			1+	19			20	21-trisomy	
42	10	11/12	Skin			15	1			16	21/21–22 translocation or isochromosome 21	38 % (Sk)
42			Blood			56	1			57		
42 Mo	30	5/12	Blood			25				25	Normal	
43		6/12	Skin				32			32	21-trisomy	Neg. (Sk)
44	3	3/12	Bone marrow				20			20	21-trisomy	
45	2	4/12	Blood I	1		9	24			34	Normal/ trisomy 21 type of mosaicism	Pos. (Or)
45			Blood II	1		15	17			33		
45			Skin I	2	3	13	13			31		Pos. (Sk)
45			Skin II			21	3			24		
45			Skin III		5	120	46			171		
45 Mo	40		Blood		1	36				37	Normal	
45 Fa	31		Blood		2	49				51	Normal	
46	2	7/12	Skin				40			40	21-trisomy	42 % (Sk)
47	42	10/12	Skin I				28	1+		29	21-trisomy	32 % (Or)
47			Skin II				12			12	21-trisomy	
48		1/12	Blood				21			21	21-trisomy	Neg. (Or)
49	1	0/12	Bone marrow			1+	34	1+		36	21-trisomy	Neg. (BM)
49			Skin				15			15	21-trisomy	
50		7/12	Skin				32			32	21-trisomy	32 % (Or)
51		4/12	Bone marrow			1+	38			39	21-trisomy	Neg. (Or)
52		4/12	Bone marrow						49	49	21-trisomy plus an extra small meta-centric chromosome	42 % (Sk)
52			Skin				2	113		115		
52 Mo	26	2/12	Skin		1*	39				40	Normal	33 % (Sk)
52 Fa	31	10/12	Skin			34				34	Normal	Neg. (Sk)
53		<1/12	Blood			1+	11			12	21-trisomy	
53 Mo	39	0/12	Blood		2*	21				23	Normal	

Table I (*continued*)

Case number	Age at the time of chromosome investigation, years	Type of tissue cultured	No. of cells with chromosome count: <45	45	46	47	48	Total number of counted and analysed cells	Karyotype interpretation	Sex chromatin
54	8/12	Blood			3+	23		26	21-trisomy	
55	1 2/12	Blood			1+	20		21	21-trisomy	
56	1 1/12	Blood			1+	21		22	21-trisomy	
57	3/12	Blood				29		29	21-trisomy	
58	1/12	Blood				23		23	21-trisomy	
58 Mo	40 8/12	Blood	1	1*	26			28	Normal	
58 Fa	37 10/12	Blood	1		18			19	Normal	
59	6 10/12	Blood				29		29	21-trisomy	
60	7 8/12	Blood				27		27	21-trisomy	
61	2/12	Blood				29		29	21-trisomy	
62	<1/12	Blood		1	17			18	13–15/21 trans-location	41 % (Sk)
62		Skin		1	60			61		
62 Mo	27 7/12	Blood			40		1*	41	Normal	
		Skin			30			30	Normal	
62 Fa	26 2/12	Blood			34			34	Normal	
		Skin			30			30	Normal	
63	<1/12	Blood				18		18	21-trisomy	30 % (Sk)
63		Skin			1+	48		49	21-trisomy	
64	2/12	Skin		1+	1+	40		42	21-trisomy	Neg. (Sk)
65	1/12	Bone marrow				18		18	21-trisomy	Neg. (Sk)
65		Skin				17		17	21-trisomy	
66	<1/12	Skin			2+	40		42	21-trisomy	43 % (Sk)

67		< 1/12	Bone marrow		15		15	21-trisomy	40 % (Sk)
67			Skin	1+	20		21	21-trisomy	
68		11/12	Bone marrow		23		23	21-trisomy	55 % (BM)
68			Skin		18		18	21-trisomy	
68 Mo	26	8/12	Blood	1*	44		45	Normal	
68 Fa	32	1/12	Blood		40		40	Normal	
69	6	4/12	Blood	1+	23		24	21-trisomy	Neg. (Or)
70	7	11/12	Blood	1+	39		40	21-trisomy	
71	15	3/12	Blood		20		20	21-trisomy	31 % (Or)
72	13	6/12	Blood	1+	22		23	21-trisomy	32 % (Or)
73	15	10/12	Blood		24		24	21-trisomy	Neg. (Or)
74		< 1/12	Blood		20		20	21-trisomy	
75			Blood	2+	9		11	21-trisomy	
75		1/12	Skin		65	1+	66	21-trisomy	Neg. (Sk)
76	33	9/12	Blood		25		25	21-trisomy	
77	12	6/12	Blood		27		27	21-trisomy	
78	18	0/12	Blood	1+	22		23	21-trisomy	
79	21	9/12	Blood	1+	24		25	21-trisomy	
80	53	5/12	Blood	1+	24		25	21-trisomy	Neg. (Sk)
80			Skin	1+	28		29	21-trisomy	Neg. (Or)
81	16	7/12	Blood	3+	35		38	21-trisomy	
81 Mo	43	0/12	Blood		43		43	Normal	
81 Br	15	9/12	Blood	1*	46	2*	49	Extra small chromosome	Neg. (Or)
81 Br			Skin	1*	38		39	Extra small chromosome	Neg. (Sk)
82	14	7/12	Blood	1+	22		23	21-trisomy	
83		1/12	Blood	1+	19		20	21-trisomy	
84	41	8/12	Blood	1+	44		45	21-trisomy	
85	27	6/12	Skin		10		10	21-trisomy	

Table I (*continued*)

Case number	Age at the time of chromosome investigation, years	Type of tissue cultured	No. of cells with chromosome count: <45	45	46	47	48	Total number of counted and analysed cells	Karyotype interpretation	Sex chromatin
85		Spleen				14		14	21-trisomy	
85		Brain				20		20	21-trisomy	
86	21 0/12	Blood				29		29	21-trisomy	
87	22 0/12	Blood				35		35	21-trisomy	
88	23 9/12	Blood		2	32			34	21/21–22 translocation or isochromosome 21	33 % (Or)
88 Mo	48 6/12	Blood		1*	33			34	Normal	
88 Fa	48 9/12	Blood			34			34	Normal	
89	17 0/12	Blood				33		33	21-trisomy	
90	< 1/12	Blood				30		30	21-trisomy	
91	20 3/12	Blood			1+	24		25	21-trisomy	
92	25 0/12	Blood				25		25	21-trisomy	
93	15 4/12	Blood			1+	37		38	21-trisomy	
94	< 1/12	Blood			1+	29		30	21-trisomy	
95	< 1/12	Blood I			1+	15		16	21-trisomy	
95		Blood II			1+	23		24	21-trisomy	
96	< 1/12	Blood I			1+	9		10	21-trisomy	
96		Blood II				31		31	21-trisomy	
97	1/12	Blood				55		55	21-trisomy	
97		Skin			1+	37		38	21-trisomy	60 % (Sk)
97 Mo	32 6/12	Blood		1	27			28	Normal	

98	5	10/12	Blood			30	30	21-trisomy	
98 Mo	32	9/12	Blood	1	39		40	Normal	
98 Fa	42	0/12	Blood		40		40	Normal	
98 Br	4	1/12	Bone marrow	1*	23		24	Chromatid breaks in 2 cells otherwise normal	
98 Br			Blood	1*	36		37	Chromatid breaks in 5 cells otherwise normal	
99	3	1/12	Skin			39	39	21-trisomy	36 % (Sk)
99 Mo	26	6/12	Blood		45		45	Normal	
99 Fa	30	2/12	Blood	1	34		35	Normal	
100	45	4/12	Blood			20	20	21-trisomy	
101	21	2/12	Blood			30	30	21-trisomy	
102		< 1/12	Blood	2	41		43	21/21–22 translocation or isochromosome 21	
102			Bone marrow		44		44		
102			Skin		29		29		Neg. (Sk)
102 Mo	36	0/12	Blood		45		45	Normal	
102 Fa	50	11/12	Blood		45		45	Normal	
103	32	9/12	Blood			30	30	21-trisomy	

TABLE II. *Cytogenetical data of the patients with clinically suspected Down's syndrome who were found to have apparently normal karyotypes (Cases S 1–S 16).*

Case number	Age at the time of chromosome investigation, years	Type of tissue cultured	No. of cells with chromosome count: 45	46	47	48	Total number of counted and analysed cells	Karyotype interpretation	Sex chromatin
S 1	9/12	Bone marrow		17			17	Normal	Neg. (Or)
S 2	27 7/12	Bone marrow I		20			20	Normal	Neg. (Or)
S 2		Bone marrow II		7			7	Normal	
S 3	4/12	Bone marrow		19			19	Normal	
S 4	11/12	Bone marrow		11			11	Normal	31 % (Or)
S 4		Skin		14			14	Normal	
S 5	6 10/12	Skin		21			21	Normal	Neg. (Sk)
S 6	< 1/12	Skin		24			24	Normal	38 % (Sk)
S 7	11 10/12	Skin		25			25	Normal	Neg. (Sk)
S 8	16 10/12	Skin		17			17	Normal	Neg. (Sk)
S 9	2 0/12	Bone marrow I	2*	41	1*		44	Normal	53 % (BM)
S 9		Bone marrow II		31	1*		32	Normal	
S 9		Skin	1*	23			24	Normal	
S 10	7 0/12	Blood		32			32	Normal	36 % (Or)
S 11	4 10/12	Blood		17			17	Normal	35 % (Sk)
S 11		Skin	1*	20			21	Normal	
S 12	< 1/12	Bone marrow	1*	22			23	Normal	33 % (BM)
S 13	8/12	Blood	1*	21			22	Normal	Neg. (Or)
S 14	8 0/12	Skin		23			23	Normal	50 % (Sk)
S 15	1 11/12	Skin	1*	28			29	Normal	38 % (Sk)
S 16	8 0/12	Blood		30			30	Normal	Neg. (Or)
S 16		Skin		30			30	Normal	

TABLE III. *Cytogenetical data of some patients with chromosomal aberrations resembling those found in Down's syndrome (Cases I–IV).*

Case number	Type of tissue cultured	No. of cells with chromosome count: 45	46	47	48	Total number of counted cells	No. of photographed and analysed cells	Karyotype interpretation	Sex chromatin
I (Cases I and II are sibs)	Blood I		1	18	2	21	14		36 % (Or)
I	Blood II			20		20	12		
II	Blood		1	14		15	5		
II	Skin			13		13		Extra small autosome	35 % (Sk)
II	Spleen		1	48	3	52	8		
II	Bone marrow		1	30	1	32	4		38 % (BM)
II	Brain			9	1	10	1		
II	Ovary			17		17	7		34 % (Ovary)
II	Intestine			13	1	14			
I–II Mo	Blood	1*	42	2*	1*	46	6	Normal	32 % (Or)
I–II Fa		1*	21			22	6	Normal	Neg. (Or)
I–II Si		1*	13			14	4	Normal	33 % (Or)
III	Bone marrow			1	64	65	17	Trisomy (13–15) + extra small chromosome	Neg. (BM)
III Mo	Blood	1*	40	1*		42	4	Normal	34 % (Or)
III Fa	Blood		30			30		Normal	Neg. (Or)
IV	Skin I	1	64	1		66	10	4–5/21–22 translocation	
IV	Skin II		10			10	4	4–5/21–22 translocation	Neg. (Sk)
IV	Bone marrow	1	24	1		26	1	4–5/21–22 translocation	
IV Mo	Skin	2	49			51	16	4–5/21–22 translocation-heterozygote	45 % (Sk)
IV Fa	Skin		15			15	1	Normal	Neg. (Sk)
IV Maternal grandfather	Blood		26			26	4	4–5/21–22 translocation-heterozygote	Neg. (Or)

TABLE IV. *Clinical data of patients with Down's syndrome*

Data / Case no.	1	2	3	4	5	6	7	8
1. Sex (M = male, F = female)	M	M	F	M	M	F	M	M
2. Reason for chromosomal investigation	T	T	T	S	T	S	T	Y
3. Age in years: months at the time of physical exam.	13:10	22:5	33:4	2:8	0:0	6:0	11:11	2:6
4. Height, cm	134	165	144	84	50	108	121	84
5. Head circumference, cm	50	54	49	45	32	47	53	47
6. Cephalic index	82	84	84	86	✕	84	83	83
7. Oblique palpebral fissures	−	+	+	+	+	−	+	+
8. Epicanthic eye-folds	−	+	−	+	+	+	+	(+)
9. Blepharitis	−	−	+	−		+	+	+
10. Brushfield spots	+	−	+	+		−	−	+
11. Flat nasal bridge	−	−	+	+		+	−	+
12. Mouth permanently open	+	−	+	+		−	−	−
13. Abnormal size, shape and alignment of teeth	+	+	+	−		−	+	+
14. Protruding tongue	+	−	+	−		−	−	−
15. Furrowed tongue	+	+	+	−		−	−	−
16. High-arched palate	−	+	+	+		+	+	+
17. Narrow palate	−	+	+	+		−	+	+
18. Folded ears	−	−	−	+		−	(+)	(+)
19. Short and broad hands	+	−	+	+		+	+	+
20. Short 5th fingers	−	−	−	+		+	+	+
21. Incurved 5th fingers	−	−	−	+		−	+	+
22. Type of four-finger line, left/right (Fig. 5)	o/o	o/o	o/o	o/o	3/o	o/o	o/o	o/o
23. Gap between 1st and 2nd toes bilaterally	+	+	(+)	+		−	+	+
24. Congenital heart defect	−	−	−	+	+		-	-
25. Hyperflexibility of joints	+	+	+	+	+	−	+	+
26. Muscular hypotonia	−	+	+	+	+	−	+	+
27. Abnormal middle phalanx of the 5th finger						−	−	+
28. Maternal age at birth of case, years	40	37	43	23	38	27	41	22
29. Paternal age at birth of case, years	35	30	40	27	50	31	43	24
30. Order in sibship	2/2	2/2	4/4	2/2	3/3	1/1	4/4	1/1
31. Weight at birth, g	2900	3000	3200	2570	3000	3520	2725	2790
32. Height at birth, cm	50	50		46	50	47	48	49
33. Born before (−) or after (+) term, days	−7	−21	±0	−10	−17	±0	±0	±0

or suspected Down's syndrome with chromosomal aberrations.

9	10	11	12	13	14	15	16	17	18	19	20	
F	M	M	M	M	F	F	M	F	M	M	F	1
Y	S	S	S	S	T	Y	S	S	T	S	Y	2
0:1	5:2	0:10	1:0	1:1	3:5	0:7	3:2	2:6	0:8	3:5	2:4	3
	96	71	68	81	89		86	75	71	87	87	4
	47	44	44	45	47		49	46	46	48	46	5
✳	85	87	92	87	93	✳	80	79	83	80	78	6
+	+	+	+	+	+	+	+	+	+	+	+	7
	+	−	+	+	−		−	+	(+)	−	(+)	8
	−	+	−	−	+		−	+	−	+	−	9
	+	+	−	+	+		+	+	+	+	−	10
+	+	+	+	+	+		−	+	+	+	+	11
	−	−	−	+	−		−	+	+	+	+	12
	−	−		+	−		+	−		+		13
	−	−	−	−	−	+	·	+	+	−	·	14
	+	−	−	−	−		−	−	+	·	−	15
	−	−	−		−		−	+		−	+	16
	−	−	+		−		−	+	−	−	+	17
	−	·	−	−	−		−	−	−	−		18
−	+	+	+	+	+	+	+	+	+	+	−	19
−	−	−	−	+	+	+	+	+	+	+	·	20
	−	−	−	+	+	+	+	+	+	−	+	21
	0/0	1/0	3/1	0/0	1/0	3/0	3/1	0/3	1/1	3/1	3/0	22
	+	+	+	+	+		+	+	−	+	+	23
	−	+	+	−	−	−	−	−	−	−	−	24
+	+	+	+	+	+		+	+	+	+	+	25
+	+	+	+	+	+		+	+	+	+	+	26
	−	+		−	+		+	+	+			27
24	42	38	32	42	39	26	34	32	42	27	29	28
25	28	32	31	42	37	31	39	35	36	28	30	29
1/2	3/3	3/3	3/3	1/2	4/4	1/2	6/6	2/3	1/1	3/3	2/3	30
3250	4460	3200	2100	2980	3180	3000	2450	3040	4250	3400	3230	31
49	54	51	45	47	49	47	50	49	53	49	48	32
+25	−21	−28	+4	−21	+0	−11	−25	−9	±0	−7	−21	33

Table IV (*continued*)

Data	Case no.	21	22	23	24	25	26	27	28
1. Sex (M = male, F = female)		M	M	F	F	M	F	F	M
2. Reason for chromosomal investigation		S	S	T	T	S	Y	S	F
3. Age in years: months at the time of physical exam.		2:6	2:3	0:2	9:0	1:11	0:4	0:1	15:4
4. Height, cm		78	77		121	73	57	48	145
5. Head circumference, cm		46	45		48	47	39	35	50
6. Cephalic index		80	85	✳	87	76	89	81	95
7. Oblique palpebral fissures		+	+	+	+	+	+	+	−
8. Epicanthic eye-folds		·	+	+	−	−	+	+	+
9. Blepharitis		+	−		−	−	+	−	−
10. Brushfield spots		+	+		+	+	+	−	+
11. Flat nasal bridge		+	+	+	+	+	−	+	+
12. Mouth permanently open		+	−		+	+	+	+	·
13. Abnormal size, shape and alignment of teeth		+				−			−
14. Protruding tongue		−	−	+	+	+	+	−	+
15. Furrowed tongue		−	−		+	−	−	−	+
16. High-arched palate		+			+	+		−	+
17. Narrow palate		+	+		+	+	−	−	+
18. Folded ears			−		−	−	−	+	+
19. Short and broad hands		+	+	+	+	+	−	−	+
20. Short 5th fingers		+	+	+	+	−	+	+	+
21. Incurved 5th fingers		+	+	+	−	(+)	+	+	+
22. Type of four-finger line, left/right (Fig. 5)		0/0	3/3		0/0	0/0	3/3	0/1	0/1
23. Gap between 1st and 2nd toes bilaterally		+	(+)		+	+	+	+	+
24. Congenital heart defect		+	−	+	−	−	+	·	−
25. Hyperflexibility of joints		+	+	+	+	+	+	+	·
26. Muscular hypotonia		+	+	+	+	+	+	+	−
27. Abnormal middle phalanx of the 5th finger			+		−	+	−	+	
28. Maternal age at birth of case, years		39	30	40	39	32	27	25	31
29. Paternal age at birth of case, years		41	32		35	32	33	28	31
30. Order in sibship		4/4	2/2	1/1	3/3	5/5	2/2	4/4	2/3
31. Weight at birth, g		2410	3800	3110	2930	3300	3660	2070	2790
32. Height at birth, cm		45	50	46	50	51	49	47	46
33. Born before (−) or after (+) term, days		−10	±0	−19	±0	−7	−18	−21	−25

29	30	31	32	33	34	35	36	37	38	39	40	
M	F	M	F	F	F	F	M	M	F	M	F	1
F	F	F	F	S	S	S	S	T	S	F	F	2
11:4	25:4	24:0	22:0	6:4	1:0	0:1	1:10	0:2	1:7	15:2	13:3	3
141	145	126	147	117	68	46	82		74	149	140	4
52	50	50	50	49	44	33	45	36	46	48	51	5
94	84	84	86	85	75	92	87	✳	83	83	89	6
+	+	+	−	+	+	+	+	−	+	+	+	7
+	−	−	−	−	−	(+)	−	+	−	−	−	8
−	−	−	+	−	−	+	+		−	+	−	9
+	−	+	+	+	−	−	+	−	+	+	+	10
+	−	−	−	−	−	·	−	+	+	−	−	11
+	+	−	−	−	−	−	−		+	+	−	12
+	+	+	−	−	+		−		+	+	+	13
+	+	−	−	−	−	−	−		−	−	−	14
+	+	+	+	+	−	−	−		−	+	+	15
+	+	+	+	−	−	−	+	+	−	+	+	16
+	+	+	+	−	−	−	+	+	−	+	+	17
+	+	−	−	−	(+)	+	(+)		−	−	−	18
+	−	+	+	+	+	−	+	+	+	−	+	19
+	+	+	−	+	−	−	+	+	+	−	+	20
−	·	−		-		-	−	+	−	−	−	21
0/3	3/0	0/1	0/0	3/3	3/0	1/0	0/1	3/3	1/1	0/0	0/3	22
+	+	+	+	+	−	+	−	+	+	+	+	23
	−	-		-	−	+	−	−	−	+	+	24
+	−	+	+	+	+	+	+	+	+	−	+	25
+	−	−	−	+	+	+	+	+	−	−	+	26
					−		−	+	+			27
24	38	39	41	40	30	39	29	39	32	22	24	28
29	38	31	33	40	40	39	28	40	36	29	30	29
3/6	3/3	2/3	3/3	2/2	2/2	6/6	2/2	3/3	2/2	1/2	2/2	30
3720	2550		2500	3180	2600	3100	2050	2260	3580	3200	3450	31
51	46			50	47	44	47	45	51	50	48	32
±0	−18			±0	−30	−40	−18	±0	−7	+14	±0	33

Table IV (*continued*)

Data — Case no.	41	42	43	44	45	46	47	48
1. Sex (M = male, F = female)	M	F	M	M	F	F	F	F
2. Reason for chromosomal investigation	T	Y	Y	S	S	S	T	Y
3. Age in years: months at the time of physical exam.	14:9	11:9	1:5	4:1	2:4	3:4	43:7	0:1
4. Height, cm	106	134	74	91	84	88	137	55
5. Head circumference, cm	48	48	45	48	48	47	49	36
6. Cephalic index	82	81	87	86	75	84	86	92
7. Oblique palpebral fissures	+	+	+	+	+	+	+	+
8. Epicanthic eye-folds	+	–	–	(+)	(+)	–	–	(+)
9. Blepharitis	–	–	+	–	–	–	–	–
10. Brushfield spots	+	+	–	+	–	+	–	+
11. Flat nasal bridge	–	+	+	+	+	+	–	+
12. Mouth permanently open	–	–	+	+	–	+	–	–
13. Abnormal size, shape and alignment of teeth	+	–	+	+	–	+		
14. Protruding tongue	–	–	–	–	+	+	–	+
15. Furrowed tongue	–	+	–	–	–	–	–	–
16. High-arched palate	–	+	+	+	+	+	–	+
17. Narrow palate	–	+	+	+	+	–	–	–
18. Folded ears	+	–	–	–	–	+	–	–
19. Short and broad hands	–	–	+	+	–	+	+	–
20. Short 5th fingers	–	–	–	+	–	+	+	–
21. Incurved 5th fingers	–	–	–	+	–	–	–	–
22. Type of four-finger line, left/right (Fig. 5)	0/0	3/3	1/0	3/3	0/0	1/1	0/0	2/0
23. Gap between 1st and 2nd toes bilaterally	+	+	+	+	+	+	+	–
24. Congenital heart defect	–		–	–	–	–	–	–
25. Hyperflexibility of joints	+	–	+	–	+	+	–	+
26. Muscular hypotonia	+	–	+	–	+	+	–	+
27. Abnormal middle phalanx of the 5th finger		+		–	–	+		–
28. Maternal age at birth of case, years	37	18	18	23	38	35	33	20
29. Paternal age at birth of case, years	35		23	30	29	39	30	21
30. Order in sibship	1/1	1/2	1/1	2/2	1/1	3/3	6/8	2/2
31. Weight at birth, g	3330	2880	2840	1900	2210	3290	2500	2970
32. Height at birth, cm	51	49	48	42	46	48		49
33. Born before (–) or after (+) term, days	±0	±0	−20	−46	−2	±0		+2

49	50	51	52	53	54	55	56	57	58	59	60	
M	F	M	F	F	F	F	M	M	F	F	F	1
S	T	S	S	T	S	S	S	S	S	S	T	2
1:9	0:7	0:9	0:11	1:6	1:4	2:6	2:4	1:4	1:0	6:10	8:7	3
81	62	68	69	80	75	79	80	77	75	107	121	4
47	42	44	42	45	46	45	47	45	42	47	50	5
93	94	97	87	91	86	84	93	88	78	86	86	6
−	+	+	−	+	+	+	−	+	+	+	+	7
−	−	−	−	−	(+)	−	−	+	−	−	−	8
−	−	−	−	−	+	+	−	+	−	+	−	9
−	−	−	−	−	−	−	−	+	+	+	−	10
+	+	+	+	+	+	+	−	+	−	−	−	11
+	−	−	+	−	−	+	−	−	+	+	+	12
−				+	−	+	−	+		+	−	13
−	−	−	+	+	+	+	−	−	−	−	−	14
−	−	−	−	−	−	+	−	−	−	+	+	15
−	+	+	+	−	+	+	+	−	+	−	−	16
+	+	+	+	−	+	+	+	−	+	−	−	17
−	−	−	−	−	−	+	−	−	−	−	−	18
+	+	−	+	+	+	+	+	+	−	+	+	19
+	+	+	+	+	+	−	+	−	−	+	+	20
−	+	+	+	−	−	−	+	−	−	+	−	21
2/0	0/0	0/0	1/1	0/1	0/0	0/1	2/0	1/1	0/1	1/0	0/0	22
−	+	−	+	+	−	+	+	+	−	+	+	23
−	−	−	−	−	−	−	−	−	+	−	−	24
−	−	−	+	+	+	+	+	+	+	+	+	25
−	+	−	+	+	+	+	+	+	+	+	+	26
−	−	−		+			+	−	+	−		27
36	38	20	25	38	31	35	38	34	40	34	23	28
39	48	24	31	32	33	34	40	41	37	35	27	29
2/2	4/4	1/1	1/1	2/2	3/3	2/2	4/4	2/2	2/2	3/3	1/3	30
3790	2750	2970	2720	3870	3770	2610	2820	3350	3700	2500	3330	31
50	50	45	46	50	51	48	48	50	52	47	49	32
±0	±0	−12	−13	±0	±0	−7	±0	±0	±0	−29	±0	33

Table IV (*continued*)

Data — Case no.	61	62	63	64	65	66	67	68
1. Sex (M = male, F = female)	F	F	F	M	M	F	F	F
2. Reason for chromosomal investigation	S	S	S	T	S	S	T	S
3. Age in years: months at the time of physical exam.	1:0	0:2	0:0	0:7	0:8	0:5	0:3	1:4
4. Height, cm	66	51	51	67	67	65	60	71
5. Head circumference, cm	42	39	35	40	43	40	41	47
6. Cephalic index	92	87	87	88	93	83	83	84
7. Oblique palpebral fissures	+	+	–	+	+	+	+	–
8. Epicanthic eye-folds	+	(+)	+	+	–	+	–	+
9. Blepharitis	–	–	–	–	+	–	–	–
10. Brushfield spots	+	+	+	+	–	+	–	–
11. Flat nasal bridge	+	+	+	+	+	+	+	–
12. Mouth permanently open	+	+	–	+	+	–	+	–
13. Abnormal size, shape and alignment of teeth								–
14. Protruding tongue	+	–	–	+	+	–	+	–
15. Furrowed tongue	–	–	–	–	–	–	–	–
16. High-arched palate	–	+	–	+	–	+	+	–
17. Narrow palate	–	+	–	+	+	+	+	–
18. Folded ears	–	–	(+)	–	–	(+)	–	–
19. Short and broad hands	+	–	+	–	+	+	+	–
20. Short 5th fingers	–	–	+	–	–	–	–	–
21. Incurved 5th fingers		–	–	–	–	–	–	–
22. Type of four-finger line, left/right (Fig. 5)	0/1	0/0	0/0	2/0	0/0	1/1	0/1	3/3
23. Gap between 1st and 2nd toes bilaterally	+	+	+	+	–	+	+	+
24. Congenital heart defect	–	–	–	–	–	–	–	–
25. Hyperflexibility of joints	+	+	+	+	+	+	+	–
26. Muscular hypotonia	+	+	+	+	–	+	+	–
27. Abnormal middle phalanx of the 5th finger	+	+	+	+	+	–	–	+
28. Maternal age at birth of case, years	31	27	28	43	32	31	38	24
29. Paternal age at birth of case, years	36	26	30	50	27	34	50	29
30. Order in sibship	2/2	2/2	1/2	4/4	2/2	2/2	3/3	2/2
31. Weight at birth, g	2860	3120	3130	3700	2410	3150	4430	2580
32. Height at birth, cm	45	50	50	50	48	50	54	45
33. Born before (–) or after (+) term, days	±0	–11	±0	–25	–10	–3	±0	–9

69	70	71	72	73	74	75	76	77	78	79	80	81	
M	M	F	F	M	F	F	F	F	M	M	M	F	1
S	T	T	T	Y	Y	S	T	Y	Y	Y	T	Y	2
6:9	8:0	15:4	13:6	15:11	0:4	0:8	33:11	12:7	18:0	21:5	53:10	18:7	3
104	116	132	142	139		64	147	151	167	153	162	148	4
50	51	51	49	50	38	42	51	51	51	53	51	50	5
79	88	83	84	93	✳	88	94	77	83	83	84	79	6
+	−	+	+	+	+	+	+	−	−	+	−	+	7
+	−	(+)	+	+	+	+	−	−	−	−	−	(+)	8
+	−	−	−	−		+	+	+	+	+	+	−	9
+	+	+	+	+	−	−	+	−	+	+	+	−	10
−	−	−	−	+	+	+	−	−	−	-	−	−	11
+	−	−	+	+		+	+	+	+	−	+	+	12
+	−	+	+	+			+	+	+	+		+	13
−	−	−	+	−	+	+	−	−	+	−	−	−	14
−	+	+	+	+		−	+	+	+	+	+	−	15
+	+	−	-	+	-	-	+	+	+	-	+	+	16
+	+	+	+	+		+	+	+	+	+	-	-	17
−	−	+	−	−		−	+	+	−	−	−	−	18
−	+	−	−	+		+	+	−	−	+	+	+	19
+	+	+	+	+	+	−	−	+	+	+	+	+	20
−	−	−	+	+		−	−	+	+	+	+	+	21
0/2	2/0	0/0	1/3	3/3	0/0	0/1	0/0	1/1	3/0	0/0	2/3	0/0	22
+	+	+	+	+		+	+	+	+	+	−	+	23
−	−	-	-	-	+	−	−	−	−	+	−	+	24
+	+	+	+	+	+	+	+	+	+	−	+	+	25
+	−	+	−	−	+	+	−	+	−	−	−	+	26
−	+				−	−							27
33	43	35	32	23	21	42	39	23	21	28	38	24	28
35	42	44	36	29	26	47	42	23	24	36	35	23	29
3/3	4/4	2/4	2/2	1/1	1/1	4/4	2/2	2/2	1/2	1/2	4/4	1/2	30
2630	3030	3170	3800	2930	2720	3000	1860	3950	3460	2100		2880	31
48	49	47	52	46	47	52	43	52	52	44		49	32
±0	−12	−22	±0	±0	−9	−6	−43	−9	−20	−9		−13	33

Table IV (*continued*)

Data / Case no.	82	83	84	85	86	87	88	89	90
1. Sex (M = male, F = female)	F	F	F	F	M	F	F	M	M
2. Reason for chromosomal investigation	T	Y	T	T	T	T	Y	T	Y
3. Age in years: months at the time of physical exam.	14:11	0:5	41:10	27:6	21:1	22:2	23:11	17:1	0:2
4. Height, cm	137	60	149		160	164	144	166	
5. Head circumference, cm	50	34	53		52	51	51	52	35
6. Cephalic index	93	92	91	*	93	94	94	89	*
7. Oblique palpebral fissures	+	+	+	+	+	+	+	–	+
8. Epicanthic eye-folds	(+)	+	–	+	(+)	–	–	+	+
9. Blepharitis	+	–	+	+	+	+	+	+	
10. Brushfield spots	+	–	+		–	+	+	+	
11. Flat nasal bridge	–	+	–	+	–	–	–	–	+
12. Mouth permanently open	+	+	–		+	–	+		
13. Abnormal size, shape and alignment of teeth	+		+		+	–	–	–	–
14. Protruding tongue	+	+	–		+	–	–	–	+
15. Furrowed tongue	+	–	+	+	+	+	+	+	
16. High-arched palate	+	+	+		+	+	–	–	
17. Narrow palate	+	+	+		+	–	–	–	
18. Folded ears	–	–	–		–	+		–	
19. Short and broad hands	+	–	+	+	+	+	+	–	+
20. Short 5th fingers	+	+	–	+	+	+	+	+	+
21. Incurved 5th fingers	+	–	–	+	+	+	+	+	+
22. Type of four-finger line, left/right (Fig. 5)	o/o	3/3	o/o		o/o	o/o	o/o	3/3	o/o
23. Gap between 1st and 2nd toes bilaterally	+	+	+	+	+	+	+	+	
24. Congenital heart defect	–	–	–	+	–	–	–	–	–
25. Hyperflexibility of joints	+	+	–		+	–	–	+	+
26. Muscular hypotonia	+	+	–		+	–	–	+	+
27. Abnormal middle phalanx of the 5th finger							–		+
28. Maternal age at birth of case, years	35	25	42	35	38	35	24	36	21
29. Paternal age at birth of case, years	48	29	44	35	43	35	24	38	23
30. Order in sibship	3/4	1/1	5/5	1/2	3/3	1/1	1/2	2/2	1/1
31. Weight at birth, g	3720	3730		3250	2050	3300	3430	3020	2480
32. Height at birth, cm	50	49		50	48	51	51	49	45
33. Born before (–) or after (+) term, days	–13	±0		–3	±0	–25		–16	–27

91	92	93	94	95	96	97	98	99	100	101	102	103	
F	F	F	F	M	M	F	M	F	F	F	M	M	1
T	T	T	S	S	Y	T	T	F	T	T	S	F	2
20:7	25:2	15:6	0:1	0:5	0:0	0:2	5:10	3:5	45:7	21:3	0:1	32:10	3
148	144	147	51	58	46	53	103	94	145	152	52	164	4
50	50	49	34	39	33	36	49	48	53	52	34	53	5
89	79	85	90	86	80	88	89	95	84	87	86	79	6
+	+	+	+	+	+	+	+	+	+	+	+	−	7
−	−	−	(+)	−	+	+	(+)	−	−	−	+	+	8
−	−	−	−	−	−	−	−	+	+	+	−	+	9
−	+	+	+	+	−	−	+	−	+	+	−	−	10
−	−	−	−	−	+	+	+	+	+	−	−	+	11
−	−	−	−	+	−	−	−	−	+	+	+	−	12
	−	−	−	−	−	−	+	−		+		+	13
−	−	−	−	+	−	−	−	+	+	−	+	−	14
+	+	+	−	−	−	−	+	−	+	+	−	+	15
+	−	+	+	−	+	−	+	−	+	+	−	+	16
+	+	+	+	+	+	−	+	+	+	+	+	+	17
−	−	−	−	−	−	−	−	+	−	+	+	+	18
+	+	+	−	+	+	+	+	+	+	−	−	+	19
−	−	−	−	+	+	−	+	+	+	+	+	+	20
+	+	+	−	+	+	−	+	+	−	+	+	+	21
0/1	3/3	0/0	0/0	0/0	3/3	3/2	0/0	3/0	0/0	0/0	3/3	3/0	22
−	−	−	−	−	−	−	+	+	−	+	+	(+)	23
+	−	−	−	+	−	−	−	−	−	−	−	−	24
+	+	+	+	+	+	+	+	+	−	+	+	+	25
−	−	−	−	−	+	+	+	+	−	+	+	−	26
			−	+	+	−		+			+		27
42	38	35	42	19	22	32	26	23	44	44	36	37	28
40	49	34	40	19	21	32	35	27	49	37	50	37	29
2/2	2/2	2/3	2/2	1/1	2/2	2/2	2/3	2/2	9/9	2/2	1/1	7/9	30
2420	3300	2740	3720	2420	2230	3460	3020	3780	3250	4480	2760		31
47	51	47	48	46	45	49	50	55	50	52	49		32
−38	±0	−15	−21	−54	−16		+7	−9	±0	+25	−5		33

TABLE V. *Clinical data of patients with suspected*

Data / Case no.	S1	S2	S3	S4	S5	S6
1. Sex (M = male, F = female)	M	M	M	F	M	F
2. Reason for chromosomal investig.	S	S	S	S	S	S
3. Age in years: months at the time of physical exam.	4:0	30:4	1:0	3:5	8:10	0:1
4. Height, cm	93	162	74	98	122	47
5. Head circumference, cm	49	55	46	46	51	34
6. Cephalic index	97	82	79	83	78	83
7. Oblique palpebral fissures	+	−	−	+	−	+
8. Epicanthic eye-folds	−	+	+	−	−	−
9. Blepharitis	−	−	−	−	−	−
10. Brushfield spots	−	−	−	−	+	−
11. Flat nasal bridge	+	−	+	−	+	+
12. Mouth permanently open	+	−	·	−	−	·
13. Abnormal size, shape and alignment of teeth	−	−	−	−	−	
14. Protruding tongue	+	−	−	−	−	+
15. Furrowed tongue	−	−		−	−	
16. High-arched palate	−		−	·	·	·
17. Narrow palate	−	−	·		−	−
18. Folded ears	−	−	−	−	−	−
19. Short and broad hands	−	−	−		−	−
20. Short 5th fingers	+	+	−	−	−	
21. Incurved 5th fingers	+	+	−	+	+	−
22. Type of four-finger line, left/right[a]	3/3	0/0	0/3	0/0	0/0	0/0
23. Gap between 1st and 2nd toes bilat.	−	+	−		−	−
24. Congenital heart defect	−	−	−	−	−	+
25. Hyperflexibility of joints	+	−	−	−	−	−
26. Muscular hypotonia	+	−	−	−	−	−
27. Abnormal middle phalanx of the 5th finger	+		−	−		
28. Maternal age at birth of case, years	23	32	29	21	21	28
29. Paternal age at birth of case, years	21	45	36	29	19	40
30. Order in sibship	1/1	1/1	3/3	2/2	1/3	3/3
31. Weight at birth, g	3310	3270	4000	2410	2720	2190
32. Height at birth, cm	45	49	52	44	45	45
33. Born before (−) or after (+) term, days	±0	−15	+12	−38	±0	

[a] See Fig. 5 for explanation of types of four-finger lines.

S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	
M S	M S	F S	F S	F S	F S	M S	F S	F S	M S	1 2
12:8	18:3	2:10	7:0	4:11	0:5	2:2	8:0	2:0	8:3	3
142	168	82	119	97	68	85	126	85	130	4
53	53	47	48	46	42	52	50	45	51	5
86	79	97	76	73	82	96	75	83	93	6
–	–	–	–	–	+	+	–	–	–	7
–	–	–	–	–	–	–	–	–	–	8
–	–	–	–	–	–	+	–	–	–	9
–		–	–	–	–	–	–	–	–	10
–	–	–	–	–	–	–	–	–	–	11
–	–	–	–	–	–	–	+	–	–	12
–	–	–	–	+		–	–	–	–	13
–	–	–	–	–	–	–	–	–	–	14
–	–	–	–	–	–	–	–	–	–	15
–	–	–	–	–	–	–	–	–	–	16
–	–	–	–	+	–	–	–	–	–	17
–	–	–	–	–	–	–	–	–	–	18
–	–	–	–	–	–	–	–	–	–	19
–	–	–	–	+	–	–	–	–	–	20
–	–	–	–	–	–	–	+	–	–	21
0/0	3/3	3/0	0/1	0/0	0/0	0/1	3/0	0/0	0/0	22
+	+	–	+	–	–	+	+	–	–	23
–	–	–	–	–	–	–	+	–	–	24
–	–	–	–	+	–	–	–	–	+	25
–	–	–	–	–	–	–	+	–	+	26
		–	–	–	–	–	–	–	–	27
36	24	23	35	37	35	35	30	21	29	28
40	23	31	33	42	34	42	29	22		29
2/2	1/2	3/3	3/5	3/4	3/3	2/2	1/1	1/1	3/3	30
2930	4600	3960	3200	3260	4700	4750	2220	3400	3200	31
47		49	50	50	55	55	47	47	47	32
−22	±0	+16	+17	+18	+12	±0	±0	+21	+2	33

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AKADEMISK AVHANDLING

som med vederbörligt tillstånd av
Medicinska Fakulteten vid Uppsala Universitet
för vinnande av medicine doktorsgrad offentligen försvaras
å Patologiska Institutionens i Uppsala föreläsningssal
lördagen den 4 april 1964 kl. 9 f.m.

AV

KARL-HENRIK GUSTAVSON
MED. LIC., ÖSTG.

UPPSALA 1964
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